Appendix A. Search Strategies for Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer

Primary Search Strategy (Ovid MEDLINE)

1. exp Urinary Bladder Neoplasms/
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (cis or Tis or ta or t1$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 1 and 6
8. exp Biological Markers/
9. 7 and 8
10. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. 7 and 10
12. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. exp Surgical Procedures, Operative/
14. exp Drug Therapy/
15. exp Antineoplastic Agents/
16. exp Radiotherapy/
17. (th or su or rt or dh or dt).fs.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18
20. 7 and 19
21. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,

protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

22. 7 and 21
23. (electromotiv$ or emda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 1 and 23
25. (blue adj5 cystoscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26. 1 and 25
27. exp Radiotherapy/
28. rt.fs.
29. 27 or 28
30. 7 and 29
31. 9 or 11 or 20 or 22 or 24 or 26 or 30
32. exp Urinary Bladder Neoplasms/
33. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
34. (t2$ or t3$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
35. 33 or 34
36. 32 and 35
37. cystectom$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
38. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. 37 or 38
40. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
41. (avoid$ adj7 cystectom$).mp.
42. 40 or 41
43. exp Lymph Node Excision/
44. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
45. 43 or 44

46. (adjuvant$ or neoadjuvant$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
47. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
48. 46 or 47
49. 39 or 42 or 45 or 48
50. 36 and 49
51. 31 or 50
52. limit 51 to yr="1990 -Current"
53. limit 52 to english language
54. limit 52 to abstracts
55. 53 or 54

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. (cis or Tis or ta or t1$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13. Antineoplastic$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. (t2$ or t3$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

37. (adjuvant$ or neoadjuvant$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41
43. limit 42 to yr="1990 -Current"

Database: EBM Reviews – Cochrane Database of Systematic Reviews

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, abstract, full text, keywords, caption text]

Database: EBM Reviews – Database of Abstracts of Reviews of Effects

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, full text, keywords]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, full text, keywords]
3. (cis or Tis or ta or t1$).mp. [mp=title, full text, keywords]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, full text, keywords]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, full text, keywords]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, full text, keywords]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, full text, keywords]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, full text, keywords]

13. Antineoplastic$.mp. [mp=title, full text, keywords]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, full text, keywords]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, full text, keywords]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, full text, keywords]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, full text, keywords]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, full text, keywords]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, full text, keywords]
27. (t2$ or t3$).mp. [mp=title, full text, keywords]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, full text, keywords]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, full text, keywords]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, full text, keywords]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, full text, keywords]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, full text, keywords]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, full text, keywords]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Database: EBM Reviews – Health Technology Assessment

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]

Appendix A. Search Strategies for Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer

Database: EBM Reviews – NHS Economic Evaluation Database

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, text, subject heading word]
3. (cis or Tis or ta or t1$).mp. [mp=title, text, subject heading word]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, text, subject heading word]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, text, subject heading word]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, text, subject heading word]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, text, subject heading word]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, text, subject heading word]
13. Antineoplastic$.mp. [mp=title, text, subject heading word]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, text, subject heading word]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, text, subject heading word]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, text, subject heading word]
21. 1 and 20 (0)
22. (blue adj5 cystoscop$).mp. [mp=title, text, subject heading word]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, text, subject heading word]
27. (t2$ or t3$).mp. [mp=title, text, subject heading word]
28. 26 or 27

29. 25 and 28
30. cystectom$.mp. [mp=title, text, subject heading word]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, text, subject heading word]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, text, subject heading word]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, text, subject heading word]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, text, subject heading word]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, text, subject heading word]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Appendix B. PICOTS

PICOT	Inclusion and Exclusion Criteria
Populations	Include: • Patients with signs or symptoms of possible bladder cancer [KQ 1; KQ 6; KQ7] • Patients with non-muscle invasive bladder cancer (stages Ta, Tis, or T1) [KQ 2] • Adults with non-muscle invasive bladder cancer treated with TURBT [KQ 3; KQ 8] • Adults with high-risk non-muscle invasive bladder cancer treated with TURBT [KQ4; KQ8] • Adults undergoing surveillance following treatment for non-muslce invasive bladder cancer [KQ 1; KQ 5; KQ 6; KQ 7]
Interventions	Include: • Urinary biomarkers [KQ 1; KQ 5; KQ 7] • Risk-adapted treatment approaches [KQ 2] • Intravesical chemotherapeutic or immunotherapeutic agents [KQ 3; KQ 8] • External beam radiation therapy, with or without systemic chemotherapy or immunotherapy [KQ 4] • Blue light cystoscopy or other methods of augmented cystoscopy • Biomarkers included are: BTAstat® [BTA], Alere NMP22®, BladderChek® [NMP22], UroVysion® [FISH] and ImmunoCyt™ [immunocytology], CxBladder™ • Chemotherapeutic and immunotherapeutic agents of interest include: mitomycin; apaziquone; paclitaxel; gemcitabine; thiotepa; valrubicin; doxorubicin; epirubicin; bacillus Calmette-Guérin (BCG); and interferon Exclude: • Electromotive drug administration
Comparators	Include: • Other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology and imaging) [KQ 1; KQ 5; KQ 7] • Treatment not guided by risk-adapted approach [KQ 2] • Other Intravesical chemotherapeutic or immunotherapeutic agent, different dose or duration of intravesical chemotherapy or immunotherapy, or TURBT alone [KQ 3; KQ 8] • Intravesical chemotherapeutic or immunotherapeutic agents or cystectomy. [KQ 4]
Outcomes	Include: • Diagnostic accuracy, using cystoscopy with biopsy as the reference standard [KQ 1; KQ 5] • Mortality, disease specific and all-cause [KQ 2; KQ 3; KQ 4; KQ 5] • Need for cystectomy [KQ 2; KQ 3; KQ 4; KQ 5] • Recurrence of cancer [KQ 2; KQ 3;' KQ 4; KQ 5; KQ 6] • Progression of cancer [KQ 2; KQ 3; KQ 4; KQ 5] • Quality of life [KQ 2; KQ 3; KQ 4; KQ 5] • Adverse effects of diagnostic testing [KQ 7] • Adverse effects of treatment [KQ 8] Exclude: • Prediction of treatment response
Timing	Include: • Any duration of followup
Setting	Include: • Inpatient or outpatient settings
Study Design	Include: • RCTs, Cohort Studies Must be comparative • Systematic reviews Must evaluate quality of individual studies

KQ, key question; PICOTS=populations, interventions, comparators, outcomes, timing, setting; TURBT, transurethral resection of bladder tumor

Appendix C. Included Studies

Addeo R, Caraglia M, Bellini S, et al. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. J Clin Oncol. 2010 Feb 1;28(4):543-8. PMID: 19841330.

Akaza H, Isaka S, Koiso K, et al. Comparative analysis of short-term and long-term prophylactic intravesical chemotherapy of superficial bladder cancer. Prospective, randomized, controlled studies of the Japanese Urological Cancer Research Group. Cancer Chemother Pharmacol. 1987;20 Suppl:S91-6. PMID: 3117403.

Akaza H, Koiso K, Kotake T, et al. Long-term results of intravesical chemoprophylaxis of superficial bladder cancer: experience of the Japanese Urological Cancer Research Group for Adriamycin. Cancer Chemother Pharmacol. 1992;30 Suppl:S15-20. PMID: 1394810.

Ali-el-Dein B, el-Baz M, Aly AN, et al. Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stages pTa and pT1): a randomized prospective study. J Urol. 1997 Jul;158(1):68-73; discussion -4. PMID: 9186325.

Ali-el-Dein B, Nabeeh A, el-Baz M, et al. Single-dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transurethral resection of pTa and pT1 transitional-cell bladder tumours: a prospective, randomized controlled study. Br J Urol. 1997 May;79(5):731-5. PMID: 9158511.

Ali-El-Dein B, Nabeeh A, Ismail EH, et al. Sequential bacillus Calmette-Guerin and epirubicin versus bacillus Calmette-Guerin alone for superficial bladder tumors: a randomized prospective study. J Urol. 1999 Aug;162(2):339-42. PMID: 10411034.

Au JL, Badalament RA, Wientjes MG, et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst. 2001 Apr 18;93(8):597-604. PMID: 11309436.

Babjuk M, Soukup V, Petrik R, et al. 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. BJU Int. 2005 Oct;96(6):798-802. PMID: 16153204.

Bassi P. Dose Response of Bacillus Calmette-Guerin (BCG) in superficial bladder cancer: a phase III randomized tial low-dose vs standard-dose BCG regimen. J Urol. 1992;146:32-5. PMID: No PMID.

Berrum-Svennung I, Granfors T, Jahnson S, et al. A single instillation of epirubicin after transurethral resection of bladder tumors prevents only small recurrences. J Urol. 2008 Jan;179(1):101-5; discussion 5-6. PMID: 17997459.

Bilen CY, Ozen H, Aki FT, et al. Clinical experience with BCG alone versus BCG plus epirubicin. Int J Urol. 2000 Jun;7(6):206-9. PMID: 10843451.

Boccardo F, Cannata D, Rubagotti A, et al. Prophylaxis of superficial bladder cancer with mitomycin or interferon alfa-2b: results of a multicentric Italian study. J Clin Oncol. 1994 Jan;12(1):7-13. PMID: 8270987.

Bohle A, Leyh H, Frei C, et al. Single postoperative instillation of gemcitabine in patients with non-muscle-invasive transitional cell carcinoma of the bladder: a randomised, double-blind, placebo-controlled phase III multicentre study. Eur Urol. 2009 Sep;56(3):495-503. PMID: 19560257.

Bouffioux C, Kurth KH, Bono A, et al. Intravesical adjuvant chemotherapy for superficial transitional cell bladder carcinoma: results of 2 European Organization for Research and Treatment of Cancer randomized trials with mitomycin C and doxorubicin comparing early versus delayed instillations and short-term versus long-term treatment. European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol. 1995 Mar;153(3 Pt 2):934-41. PMID: 7853578.

Burger M, Stief C, Zaak D, et al. Does photodynamic TURB improve outcome of intitial T1 high grader bladder cancer? Long-term follow-up of a randomised study. European Urology Supplements. 2008;7(3):299. PMID: No PMID.

Cai T, Nesi G, Tinacci G, et al. Can early single dose instillation of epirubicin improve bacillus Calmette-Guerin efficacy in patients with nonmuscle invasive high risk bladder cancer? Results from a prospective, randomized, double-blind controlled study. J Urol. 2008 Jul;180(1):110-5. PMID: 18485394.

Chahal R, Darshane A, Browning AJ, et al. Evaluation of the clinical value of urinary NMP22 as a marker in the screening and surveillance of transitional cell carcinoma of the urinary bladder. Eur Urol. 2001 Oct;40(4):415-20; discussion 21. PMID: 11713396.

Cheng CW, Chan PS, Chan LW, et al. 17-year follow-up of a randomized prospective controlled trial of adjuvant intravesical doxorubicin in the treatment of superficial bladder cancer. Int Braz J Urol. 2005 May-Jun;31(3):204-11. PMID: 15992422.

Cheng CW, Chan SFP, Chan LW, et al. Twelve-year follow up of a randomized prospective trial comparing bacillus Calmette-Guerin and epirubicin as adjuvant therapy in superficial bladder cancer. Int J Urol. 2005 May;12(5):449-55. PMID: 15948743.

Cho DY, Bae JH, Moon DG, et al. The effects of intravesical chemoimmunotherapy with gemcitabine and Bacillus Calmette-Guerin in superficial bladder cancer: a preliminary study. J Int Med Res. 2009 Nov-Dec;37(6):1823-30. PMID: 20146880.

Appendix C. Included Studies

Cookson MS, Herr HW, Zhang ZF, et al. The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol. 1997 Jul;158(1):62-7. PMID: 9186324.

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Appendix D. Excluded Studies

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Gruschwitz T, Grimm MO. Studieearly recognition in urology. Früherkennung in der urologie. 2012;18(3):243-7. PMID: No PMID Excluded for not English language, but possibly relevant.

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Appendix D. Excluded Studies

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Institute of Applied Health Sciences. Systematic review of the clinical and cost-effectiveness, and economic evaluation, of photodynamic diagnosis and novel urine biomarker tests in the detection and follow-up of bladder cancer (Project record). Health Technology Assessment Database. 2013(4)PMID: No PMID Excluded for wrong publication type (letter, editorial, non-systematic review article).

Isaka S, Okano T, Shimazaki J, et al. Prophylaxis of superficial bladder cancer with instillation of adriamycin or mitomycin C. Cancer Chemother Pharmacol. 1987;20 Suppl:S77-80. PMID: 3117401 Excluded for wrong study design for Key Question.

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Appendix D. Excluded Studies

Jancke G, Damm O, Rosell J, et al. Risk factors for local recurrence in patients with pTa/pT1 urinary bladder cancer. Scand J Urol Nephrol. 2008;42(5):417-21. PMID: 18609266 Excluded for wrong outcome.

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Appendix D. Excluded Studies

Kehinde EO, Al-Mulla F, Kapila K, et al. Comparison of the sensitivity and specificity of urine cytology, urinary nuclear matrix protein-22 and multitarget fluorescence in situ hybridization assay in the detection of bladder cancer. Scand J Urol Nephrol. 2011 Mar;45(2):113-21. PMID: 21091091 Excluded for case-control design for biomarkers.

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Lamy A, Gobet F, Laurent M, et al. Molecular profiling of bladder tumors based on the detection of FGFR3 and TP53 mutations. J Urol. 2006 Dec;176(6 Pt 1):2686-9. PMID: 17085196 Excluded for wrong intervention.

Landman J, Chang Y, Kavaler E, et al. Sensitivity and specificity of NMP-22, telomerase, and BTA in the detection of human bladder cancer. Urology. 1998 Sep;52(3):398-402. PMID: 9730450 Excluded for wrong population.

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Li L-Y, Yang M, Zhang H-B, et al. Urinary fibronectin as a predictor of a residual tumour load after transurethral resection of bladder transitional cell carcinoma. BJU Int. 2008 Aug 5;102(5):566-71. PMID: 18410436 Excluded for wrong intervention.

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Appendix D. Excluded Studies

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Librenjak D, Situm M, Eterovic D, et al. Immunoprophylactic intravesical application of bacillus Calmette-Guerin after transurethral resection of superficial bladder cancer. Croat Med J. 2003 Apr;44(2):187-92. PMID: 12698510 Excluded for wrong study design for Key Question.

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Liew MS, Azad A, Tafreshi A, et al. USANZ: Time-trends in use and impact on outcomes of perioperative chemotherapy in patients treated with radical cystectomy for urothelial bladder cancer. BJU Int. 2013 Nov;112 Suppl 2:74-82. PMID: 24127680 Excluded for wrong comparator.

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Lipinski M, Jeromin L. Comparison of the bladder tumour antigen test with photodynamic diagnosis in patients with pathologically confirmed recurrent superficial urinary bladder tumours. BJU Int. 2002 May;89(7):757-9. PMID: 11966640 Excluded for case-control design for biomarkers.

Liu B, Zhang Y, Wang Z, et al. [Single instillation of epirubicin for the prophylaxis of recurrent primary superficial bladder carcinoma]. Chung Hua Wai Ko Tsa Chih. 2002 Feb;40(2):112-5. PMID: 11955393 Excluded for not English language, but possibly relevant.

Loo RK, Lieberman SF, Slezak JM, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. Mayo Clin Proc. 2013;88(2):129-38. PMID: 23312369 Excluded for wrong comparator.

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Maekawa S, Suzuki H, Ohkubo K, et al. [Continuous intravesical instillation of epirubicin immediately after transurethral resection of superficial bladder cancer: a prospective controlled study]. Hinyokika Kiyo. 2000 May;46(5):301-6. PMID: 10876750 Excluded for not English language, but possibly relevant.

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Appendix D. Excluded Studies

Malmstrom P-U, Sylvester RJ, Crawford DE, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. 2009 Aug;56(2):247-56. PMID: 19409692 Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

Mao Y, Zhao X, Wang S, et al. Urinary nucleosides based potential biomarker selection by support vector machine for bladder cancer recognition. Anal Chim Acta. 2007 Aug 13;598(1):34-40. PMID: 17693304 Excluded for wrong intervention.

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Melekos MD, Zarakovitis IE, Fokaefs ED, et al. Intravesical bacillus Calmette-Guerin versus epirubicin in the prophylaxis of recurrent and/or multiple superficial bladder tumours. Oncology (Williston). 1996 Jul-Aug;53(4):281-8. PMID: 8692531 Excluded for wrong population.

Menendez V, Filella X, Alcover J, et al. [Role of tissue polypeptide antigen as a marker in bladder cancer]. Actas Urol Esp. 1995 Jun;19(6):441-4. PMID: 8571803 Excluded for not English language, but possibly relevant.

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Mitin T, Hunt D, Shipley WU, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. Lancet Oncol. 2013 Aug;14(9):863-72. PMID: 23823157 Excluded for wrong intervention.

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Appendix D. Excluded Studies

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Ru Y, Dancik GM, Theodorescu D. Biomarkers for prognosis and treatment selection in advanced bladder cancer patients. Curr Opin Urol. 2011 Sep;21(5):420-7. PMID: 21814055 Excluded for wrong study design for Key Question.

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Said MT, Abomelha MS, Orkubi SA. Intravesical immunotherapy for superficial bladder cancer. Saudi Med J. 2002 Dec;23(12):1458-61. PMID: 12518191 Excluded for wrong study design for Key Question.

Salman T, el-Ahmady O, el-Shafee M, et al. The clinical value of cathepsin-D and TNF-alpha in bladder cancer patients. Anticancer Res. 1997 Jul-Aug;17(4B):3087-90. PMID: 9329608 Excluded for wrong intervention.

Samodai L, Kiss L, Kolozsy Z, et al. The efficacy of intravesical BCG in the treatment of patients with high risk superficial bladder cancer. Int Urol Nephrol. 1991;23(6):559-67. PMID: 1769787 Excluded for wrong study design for Key Question.

Sanchez-Carbayo M, Espasa A, Chinchilla V, et al. New electrochemiluminescent immunoassay for the determination of CYFRA 21-1: analytical evaluation and clinical diagnostic performance in urine samples of patients with bladder cancer. Clin Chem. 1999 Nov;45(11):1944-53. PMID: 10545064 Excluded for wrong intervention.

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Sarosdy MF, Hudson MA, Ellis WJ, et al. Improved detection of recurrent bladder cancer using the Bard BTA stat Test. Urology. 1997 Sep;50(3):349-53. PMID: 9301696 Excluded for wrong study design for Key Question.

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Sarosdy MF, Manyak MJ, Sagalowsky AI, et al. Oral bropirimine immunotherapy of bladder carcinoma in situ after prior intravesical bacille Calmette-Guerin. Urology. 1998 Feb;51(2):226-31. PMID: 9495702 Excluded for wrong intervention.

Schiffer E, Vlahou A, Petrolekas A, et al. Prediction of muscle-invasive bladder cancer using urinary proteomics. Clin Cancer Res. 2009 Aug 1;15(15):4935-43. PMID: 19602546 Excluded for wrong intervention.

Schulze M, Stotz N, Rassweiler J. Retrospective analysis of transurethral resection, second-look resection, and long-term chemo-metaphylaxis for superficial bladder cancer: indications and efficacy of a differentiated approach. J Endourol. 2007 Dec;21(12):1533-41. PMID: 18186695 Excluded for wrong study design for Key Question.

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Selmy MA, Ibrahim GH, El Serafi TI, et al. Evaluation of urinary proepithelin as a potential biomarker for bladder cancer detection and prognosis in Egyptian patients. Cancer Biomark. 2010;7(3):163-70. PMID: 21263192 Excluded for wrong intervention.

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Senovilla Perez JL, Resel Estevez L, Moreno Sierra J, et al. [Neoadjuvant chemotherapy MVAC in the treatment of infiltrating bladder carcinoma]. Actas Urol Esp. 2000 Jul-Aug;24(7):536-41. PMID: 11011443 Excluded for not English language, but possibly relevant.

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Serretta V, Vasile P, Falletta V, et al. [Conservative treatment of locally advanced bladder carcinoma: neoadjuvant chemotherapy, TUR and radiotherapy. Results in 40 patients]. Arch Ital Urol Androl. 1998 Jun;70(3 Suppl):37-40. PMID: 9707769 Excluded for not English language, but possibly relevant.

Sexton WJ, Wiegand LR, Correa JJ, et al. Bladder cancer: a review of non-muscle invasive disease. Cancer Control. 2010 Oct;17(4):256-68. PMID: 20861813 Excluded for wrong publication type (letter, editorial, non-systematic review article).

Shahin O, Thalmann GN, Rentsch C, et al. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence, progression and survival. J Urol. 2003 Jan;169(1):96-100; discussion PMID: 12478112 Excluded for wrong study design for Key Question.

Appendix D. Excluded Studies

Shang PF, Kwong J, Wang ZP, et al. Intravesical Bacillus Calmette-Guerin versus epirubicin for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2011(5):CD006885. PMID: 21563157 Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

Shariat SF, Zippe C, Ludecke G, et al. Nomograms including nuclear matrix protein 22 for prediction of disease recurrence and progression in patients with Ta, T1 or CIS transitional cell carcinoma of the bladder. J Urol. 2005 May;173(5):1518-25. PMID: 15821471 Excluded for wrong comparator.

Sharp VJ, Barnes KT, Erickson BA. Assessment of asymptomatic microscopic hematuria in adults. Am Fam Physician. 2013;88(11):747-54. PMID: 24364522 Excluded for wrong intervention.

Shelley M, Court JB, Kynaston H, et al. Intravesical Bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2009(4)PMID: No PMID Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

Shelley M, Court JB, Kynaston H, et al. Intravesical Bacillus Calmette-Guerin in Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2010(3)PMID: No PMID Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. BJU Int. 2001 Aug;88(3):209-16. PMID: 11488731 Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. Cancer Treat Rev. 2010 May;36(3):195-205. PMID: 20079574 Excluded for systematic review or meta-analysis, used as a source document only to identify individual studies.

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Sherif A, Holmberg L, Rintala E, et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol. 2004 Mar;45(3):297-303. PMID: 15036674 Excluded for wrong population.

Shinka T, Hirano A, Uekado Y, et al. [Intravesical bacillus Calmette-Guerin instillation therapy in superficial bladder cancers--clinical study on prognostic factors]. Nippon Hinyokika Gakkai Zasshi. 1990 Mar;81(3):425-32. PMID: 2359220 Excluded for not English language, but possibly relevant.

Siracusano S, Niccolini B, Knez R, et al. The simultaneous use of telomerase, cytokeratin 20 and CD4 for bladder cancer detection in urine. Eur Urol. 2005 Mar;47(3):327-33. PMID: 15716196 Excluded for wrong intervention.

Skacel M, Fahmy M, Brainard JA, et al. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. J Urol. 2003 Jun;169(6):2101-5. PMID: 12771727 Excluded for wrong study design for Key Question.

Skinner EC, Goldman B, Sakr WA, et al. SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guerin. J Urol. 2013 Oct;190(4):1200-4. PMID: 23597452 Excluded for wrong population.

Smaldone MC, Casella DP, Welchons DR, et al. Investigational therapies for non-muscle invasive bladder cancer. Expert Opin Investig Drugs. 2010 Mar;19(3):371-83. PMID: 20078248 Excluded for wrong publication type (letter, editorial, non-systematic review article).

Soloway MS, Briggman V, Carpinito GA, et al. Use of a new tumor marker, urinary NMP22, in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. J Urol. 1996 Aug;156(2 Pt 1):363-7. PMID: 8683680 Excluded for wrong study design for Key Question.

Solsona E, Iborra I, Ricos JV, et al. Carcinoma in situ associated with superficial bladder tumor. Eur Urol. 1991;19(2):93-6. PMID: 1902418 Excluded for wrong study design for Key Question.

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Appendix D. Excluded Studies

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Appendix D. Excluded Studies

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Appendix D. Excluded Studies

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Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Chahal, 2001[5] United Kingdom Moderate	NMP22 (quantitative)	Prospective	Cystoscopy with pathological Confirmation	Patients with hematuria or irritative symptoms (n=96) or undergoing surveillance for treated bladder cancer (n=115)	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Feil, 2003[6] Germany Moderate	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation	Patients suspected of having TCC (n=41), symptoms suggestive of tumor recurrence (n=46), or undergoing surveillance (n=34)	Mean age: 62 years Male: 82% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Chahal, 2001[5] United Kingdom Moderate	16/96 (17%) primary Tumor stage: 7 Ta, 5 T1, 3 T2, 1 T1 Tumor grade: 6 G1, 3 G2, 7 G3 17/115 (16%) recurrent Tumor stage: 15 Ta, 2 T1 Tumor grade: 13 G1, 3 G2, 1 G3	NMP22 (quantitative): >10 u/ml (also >3.75, >6.4, >10, >15.25)	Not reported	None reported
Feil, 2003[6] Germany Moderate	26/113 (23%) Tumor stage: 11 Ta, 8 T1, 7 T2 Tumor grade: 7 G1, 19 G2/G3	ImmunoCyt: Positive (≥1 fluorescent cell)	8 specimens "could not be evaluated"	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Chahal, 2001[5] United Kingdom Moderate	Overall: 0.33 (11/33) Ta: 0.09 (2/22) T1: 0.43 (3/7) T2: 0.33 (1/3) T3: 1.0 (1/1) G1: 0.05 (1/19) G2: 0.33 (2/6) G3: 0.50 (4/8) Primary: 0.44 (7/16) Recurrent: 0.24 (4/17) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.49 (16/33), 0.42 (14/33), 0.42 (14/33), 0.39 (13/33), 0.33 (11/33), 0.33 (11/33), 0.33 (11/33), 0.30 (10/33)	Overall: 0.92 (164/178) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.64 (114/178), 0.80 (142/178), 0.81 (144/178), 0.86 (153/178), 0.89 (158/178), 0.92 (164/178), 0.92 (164/178), 0.93 (166/178)	Overall: 4.1 Primary: Recurrent: NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 1.4, 2.1, 2.2, 2.8, 3.0, 4.1, 4.1, 4.3	Overall: 0.73 Primary: 0.62 Recurrent: 0.83 NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.80, 0.72, 0.72, 0.71, 0.75, 0.73, 0.73, 0.75
Feil, 2003[6] Germany Moderate	Overall: 0.38 (10/26) Ta: 0.18 (2/11) T1: 0.38 (3/8) T2: 0.71 (5/7) G1: 0.14 (1/7) G2: 0.43 (can't calculate n/N) G3: 0.60 (can't calculate n/N) ImmunoCyt + cytology Overall: 0.54 (14/26)	Overall: 0.84 (73/87) ImmunoCyt + cytology Overall: 0.82 (71/87)	Overall: 2.4 ImmunoCyt + cytology Overall: 3.0	Overall: 0.74 ImmunoCyt + cytology Overall: 0.56

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Chahal, 2001[5] United Kingdom Moderate	Overall: 0.44 (11/25) Primary: 0.50 (7/14) Recurrent: 0.33 (4/12) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.20 (16/80), 0.28 (14/50), 0.29 (14/48), 0.34 (13/38), 0.44 (11/25), 0.44 (11/25), 0.45 (10/22)	Overall: 0.88 (164/186) Primary: 0.89 (73/82) Recurrent: 0.87 (90/103) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.86 (114/133), 0.88 (142/161), 0.88 (144/163), 0.88 (153/173), 0.88 (164/186), 0.88 (164/186), 0.88 (166/189)	Not reported	Not reported; NMP22 kits provided by MAST Diagnostics	
Feil, 2003[6] Germany Moderate	Overall: 0.42 (10/24) ImmunoCyt + cytology Overall: 0.47 (14/30)	Overall: 0.47 (14/30) ImmunoCyt + cytology Overall: 0.86 (71/83)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Friedrich, 2002[7] Germany Moderate	BTA stat NMP22	Unclear	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (hematuria or irritative voiding symptoms) (n=70) or undergoing surveillance for superficial bladder cancer (n=45)	Age: Not reported Sex: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 30 Ta, 15 T1

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Friedrich, 2002[7] Germany Moderate	54/115 (47%) Tumor stage 25 Ta, 20 T1, 8 ≥T2, 1 CIS Tumor grade: 7 G1, 31 G2, 16 G3	BTA stat: Positive NMP22 quantitative: >10 U/l	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Friedrich, 2002[7] Germany Moderate	BTA Overall: 0.70 (38/54) Ta: 0.52 (13/25) T1: 0.85 (17/20) ≥T2: 1.00 (8/8) CIS: 0.0 (0/1) G1: 0.43 (3/7) G2: 0.68 (21/31) G3: 0.88 (14/16) NMP22 Overall: 0.69 (37/54) Ta: 0.52 (13/25) T1: 0.90 (18/20) ≥T2: 0.75 (6/8) CIS: 0.0 (0/1) G1: 0.43 (3/7) G2: 0.71 (22/31) G3: 0.75 (12/16)	BTA Overall: 0.64 (39/61) NMP22 Overall: 0.59 (36/61)	BTA Overall: 1.9 NMP22 Overall: 1.7	BTA Overall: 0.47 NMP22 Overall: 0.53

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Friedrich, 2002[7] Germany Moderate	BTA Overall: 0.63 (38/60) NMP22 Overall: 0.60 (37/62)	BTA Overall: 0.71 (39/55) NMP22 Overall: 0.68 (36/53)	BTA Trak: Not reported NMP22: 0.68 (0.95 CI 0.59 to 0.77)	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Giannopoulos, 2001[8] Greece Moderate	NMP22 (BladderChek) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients suspected of having bladder cancer based on clinical signs, symptoms, or recent imaging results (n=118) or undergoing surveillance for superficial bladder cancer (n=95)	Mean age: 66 years Male: 85% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Giannopoulos, 2001[8] Greece Moderate	118/234 (50%) Tumor stage: 57 Ta, 32 T1, 20 T2-4, 6 CIS, 3 Tx Tumor grade: 30 G1, 45 G2, 43 G3	NMP22 quantitative: >8 u/mL BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Giannopoulos, 2001[8] Greece Moderate	NMP22 Overall: 0.64 (75/118) Ta: 0.53 (30/57) T1: 0.66 (21/32) T2-4: 0.90 (18/20) CIS: 0.83 (5/6) G1: 0.50 (15/30) G2: 0.56 (25/45) G3: 0.81 (35/43) Primary: 0.69 (47/68) Recurrent: 0.56 (28/50) BTA stat Overall: 0.73 (86/118) Ta: 0.58 (33/57) CIS: 1.00 (6/6) T1: 0.78 (25/32) T2-4: 0.95 (19/20) G1: 0.50 (15/30) G2: 0.73 (33/45) G3: 0.88 (38/43) Primary: 0.74 (50/68) Recurrent: 0.72 (36/50) NMP22 + BTA stat Overall: 0.90 (106/118)	NMP22 Overall: 0.75 (87/116) BTA stat Overall: 0.65 (75/116) NMP22 + BTA stat: Not reported	NMP22 Overall: 2.6 BTA stat Overall: 2.1	NMP22 Overall: 0.48 BTA stat Overall: 0.42

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Giannopoulos, 2001[8] Greece Moderate	NMP22 Overall: 0.72 (75/104) BTA stat Overall: 0.68 (86/127)	NMP22 Overall: 0.67 (87/130) BTA stat Overall: 0.70 (75/107)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Gibanel, 2002[9] Spain Moderate	BTA TRAK	Unclear	Cystoscopy with pathological confirmation	Patients with symptoms suspicious for bladder cancer or undergoing surveillance for bladder cancer (n=65) Excluded patients with BCG therapy, radiotherapy, or intravesical mitomycin	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Previous bladder cancer stage/grade: Not reported
Grossman, 2005[10] United States (also Lotan 2009[11]) Low	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients with risk factors or symptoms associated with bladder cancer (e.g. smoking, hematuria, dysuria) (n=1331)	Mean age: 59 years Male: 57% Race: 82% White, non-Hispanic; 9% Smoker: Not reported Signs or symptoms: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Gibanel, 2002[9] Spain Moderate	21/65 (32%) Tumor stage: 2 Tis, 12 Ta, 2 T1, 5 T2-4 Tumor grade: 9 G1, 4 G2, 6 G3	BTA TRAK: >18 U/ml	Not reported	None reported
Grossman, 2005[10] United States (also Lotan 2009[11]) Low	79/1331 (5.9%) Tumor stage: 30 Ta, 27 T1, 6 T2 or T2a, 4 T3a or T3b, 7 Tx, 5 CIS Tumor grade: 27 well differentiated, 18 moderately differentiated, 25 poorly differentiated, 9 grade unknown	NMP22 qualitative: Positive	16 patients did not undergo NMP22	49 patients did not undergo cystoscopy (excluded)

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Gibanel, 2002[9] Spain Moderate	Overall: 0.52 (11/21) Ta: 0.33 (4/12) T1: 0.50 (1/2) T2-4: 1.00 (5/5) CIS: 0.50 (1/2) G1: 0.22 (2/9) G2: 0.60 (3/5) G3: 1.00 (5/5) BTA TRAK + cytology Overall: 0.81 (17/21)	Overall: 0.86 (31/36) BTA TRAK + cytology Overall: 0.83 (30/36)	Overall: 3.7 BTA TRAK + cytology Overall: 4.8	Overall: 0.56 BTA TRAK + cytology Overall: 0.23
Grossman, 2005[10] United States (also Lotan 2009[11]) Low	Overall: 0.56 (44/79) Ta: 0.47 (14/30) T1: 0.48 (13/27) T2, T2a: 1.00 (6/6) T3a, T3b: 0.75 (3/4) Tx: 0.57 (4/7) Ta-T1: 0.50 (31/62) T2-T3: 0.90 (9/10) CIS: 0.80 (4/5) Well-differentiated: 0.48 (13/27) Moderately differentiated: 0.50 (9/18) Poorly differentiated: 0.72 (18/25) Gx: 0.44 (4/9) Men: 0.59 (34/58) Women: 0.50 (9/18) <65 years: 0.63 (17/27) >65 years: 0.53 (26/49) Smoker: 0.50 (18/36) Non-smoker: 0.62 (25/40) Microhematuria: 0.47 (17/36) Gross hematuria: 0.44 (26/59)	Overall: 0.86 (1073/1252) Men: 0.84 (556/665) Women: 0.88 (466/531) <65 years: 0.89 (679/766) >65 years: 0.80 (343/430) Smoker: 0.86 (367/425) Non-smoker: 0.85 (655/771) Microhematuria: 0.86 (799/924) Gross hematuria: 0.79 (133/168)	Overall: 4.0	Overall: 0.51

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Gibanel, 2002[9] Spain Moderate	Overall: 0.69 (11/16) BTA TRAK + cytology Overall: 0.74 (17/23)	Overall: 0.76 (31/41) BTA TRAK + cytology Overall: 0.88 (30/34)	Overall: 0.68 +/- 0.079 BTA TRAK + cytology Overall: Not reported	Not reported	
Grossman, 2005[10] United States (also Lotan 2009[11]) Low	Overall: 0.20 (44/223) Men: 0.24 (34/143) Women: 0.12 (9/74) <65 years: 0.16 (17/104) >65 years: 0.23 (26/113) Smoker: 0.24 (18/76) Non-smoker: 0.18 (25/141) Microhematuria: 0.12 (17/142) Gross hematuria: 0.98 (799/818)	Overall: 0.97 (1073/1108) Men: 0.96 (556/580) Women: 0.98 (466/475) <65 years: 0.99 (679/689) >65 years: 0.94 (343/366) Smoker: 0.95 (367/385) Non-smoker: 0.98 (655/670) Microhematuria: 0.98 (799/818) Gross hematuria: 0.80 (133/166)	Not reported	Matritech Inc.	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Grossman, 2006[12] United States Low	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=668)	Mean age: 71 years Male: 75% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Gudjonsson, 2008[13] Sweden Moderate	FISH (UroVysion)	Prospective	Cystoscopy with pathological confirmation	Patients under surveillance for Ta, T1, and CIS (n=156)	Mean age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: All Ta, T1, or CIS; otherwise not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Grossman, 2006[12] United States Low	103/668 (15%) Tumor stage: 50 Ta, 17 T1, 8 T2, 1 T3, 2 T4, 8 CIS, 17 Tx Tumor grade: 38 well differentiated, 16 moderately differentiated, 32 poorly differentiated	NMP 22 qualitative: Positive	None reported	None
Gudjonsson, 2008[13] Sweden Moderate	27/152 (18%) Tumor stage/grade: 1 low malignant potential, 16 TaG1-G2, 1 TaG1 + CIS, 5 Tis, 4 T1G2-G3	FISH: Positive (>16% cells with multiple chromosomes or >48% cells with 9p21 homozygous loss)	16 patients had insufficient amounts of urothelial cells, or other technical factors	4 patients underwent electrocauterization without biopsy

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Grossman, 2006[12] United States Low	NMP22 Overall: 0.50 (51/103) Ta: 0.36 (18/50) T1: 0.65 (11/17) T2-T4: 0.91 (10/11) Tx: 0.47 (8/17) Well differentiated: 0.32 (12/38) Moderately differentiated: 0.44 (7/16) Poorly differentiated: 0.75 (24/32) NMP22 + cytology Overall: 0.99 (102/103)	NMP22 Overall: 0.87 (493/565) No evidence of urinary tract disease: 0.89 (236/264) Benign prostatic hyperplasia/prostatitis: 0.86 (103/120) Erythema/cystitis/inflammation : 0.85 (70/82) Urinary tract infection: 0 (0/3) Hyperplasia/squamous metaplasia/cyst/polyp/caruncl e: 0.91 (21/23) Calculi: 0.83 (5/6) Trabeculations: 0.88 (43/49) Diverticulum/pouch/cellule: 0.83 (15/18) NMP22 + cytology Overall: Not reported	NMP22 Overall: 3.8	NMP22 Overall: 0.57
Gudjonsson, 2008[13] Sweden Moderate	Overall: 0.30 (8/27) Low malignant potential: 0.0 (0/1) TaG1-G2: 0.06 (1/16) TaG1 + CIS: 1.00 (1/1) T1G2-G3: 0.25 (1/4) CIS: 1.00 (5/5)	Overall: 0.95 (119/125)	Overall: 6.0	Overall: 0.74

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Grossman, 2006[12] United States Low	NMP22 Overall: 0.41 (51/123)	NMP22 Overall: 0.90 (493/545)	Not reported	Matritech Inc.	Cases include 9 patients diagnosed after initial cystoscopy at 1-5 months (7 at 1-3 months)
Gudjonsson, 2008[13] Sweden Moderate	Overall: 0.57 (8/14)	Overall: 0.86 (119/138)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Gupta, 2009[14] India Moderate	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients under surveillance for NMIBC (n=145) Excluded patients with active UTI	Mean age: 57 years Male: 87% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 91 Ta, 45 T1, 9 CIS; 18 low malignant potential, 83 low grade, 44 high grade
Gutierrez Banos, 2001[15] Spain Moderate	NMP22 (quantitative) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with signs and symptoms suspicious for bladder cancer (n=64) or undergoing surveillance for bladder cancer (n=86) Excluded patients with recent systemic chemotherapy, renal disease (stones, nephritis, or kidney cancer), recent bladder trauma, radiation therapy, or gross hematuria and UTI	Mean age: 68 years Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms (n=64): 88% macroscopic hematuria, 6.2% irritative symptoms, 6.2% other Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Gupta, 2009[14] India Moderate	56/145 (39%) Tumor stage: 31 Ta, 13 T1, 3 CIS Tumor grade: 6 low malignant potential, 27 low grade, 14 high grade	NMP22 qualitative: Positive	Not reported	None reported
Gutierrez Banos, 2001[15] Spain Moderate	76/150 (51%) Tumor stage: 16 Ta, 46 T1, 14 T2- T4 Tumor grade: 16 G1, 29 G2, 31 G3	NMP22 quantitative: >10 U/ml (also >6 U/ml) BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Gupta, 2009[14] India Moderate	Overall: 0.86 (48/56) Low malignant potential: 1.00 (7/7) Low grade: 0.81 (29/36) High grade: 0.85 (11/13) NMP22 + cytology Overall: 0.93 (52/56)	Overall: 0.78 (69/89) LMP: 0.55 Low grade: 0.65 High grade: 0.57 NMP22 + cytology Overall: 0.75 (67/89)	Overall: 3.9 LMP: 2.2 Low grade: 2.3 High grade: 2.0 NMP22 + cytology Overall: 3.7	Overall: 0.18 LMP: 0 Low grade: 0.29 High grade: 0.26 NMP22 + cytology Overall: 0.09
Gutierrez Banos, 2001[15] Spain Moderate	NMP22 >10 U/ml Overall: 0.76 (58/76) Ta: 0.50 (8/16) T1: 0.80 (37/46) T2-T4: 0.93 (13/14) G1: 0.50 (8/16) G2: 0.69 (20/29) G3: 0.97 (30/31) NMP22 >6 U/ml Overall: 0.84 (64/76) Ta: 0.69 (11/16) T1: 0.85 (39/46) T2-T4: 1.00 (14/14) G1: 0.69 (11/16) G2: 0.76 (22/29) G3: 1.00 (31/31) BTA stat Overall: 0.72 (55/76) Ta: 0.50 (8/16) T1: 0.74 (34/46) T2-T4: 0.93 (13/14) G1: 0.56 (9/16) G2: 0.62 (18/29) G3: 0.90 (28/31)	NMP22 >10 U/ml Overall: 0.91 (67/74) NMP22 >6 U/ml Overall: 0.86 (64/74) BTA stat Overall: 0.89 (66/74)	NMP22 >10 U/ml Overall: 8.1 NMP22 >6 U/ml Overall: 6.2 BTA stat Overall: 6.7	NMP22 >10 U/ml Overall: 0.26 NMP22 >6 U/ml Overall: 0.18 BTA stat Overall: 0.31

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Gupta, 2009[14] India Moderate	Overall: 0.71 (48/68) LMP: 0.088 Low grade: 0.44 High grade: 0.16	Overall: 0.90 (69/77) LMP: 1.00 Low grade: 0.91 High grade: 0.97	Not reported	Not reported	Unable to calculate n/N for specificity and PPV/NPV stratified by tumor grade
Gutierrez Banos, 2001[15] Spain Moderate	NMP22 >10 U/ml Overall: 0.89 (58/65) NMP22 >6 U/ml Overall: 0.86 (64/74) BTA stat Overall: 0.87 (55/63)	NMP22 >10 U/ml Overall: 0.79 (67/85) NMP22 >6 U/ml Overall: 0.84 (64/76) BTA stat Overall: 0.76 (66/87)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Halling, 2002[16] USA High	BTA stat FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=146) or with signs and symptoms (n=119)	Mean age: 70 years Male: 75% Race: Not reported Smoker: Not reported Signs and symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Ianari, 1997[17] Italy Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=75)	Median age: 66 years Male: 83% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Halling, 2002[16] USA High	75/265 (28%) Tumor stage: 38 Ta, 19 T1-T4, 17 CIS Tumor grade: 12 G1, 25 G2, 37 G3	BTA stat: positive FISH: Positive (>5 cells with gains of ≥2 chromosomes or ≥10 cells with gains of 1 chromosome, or >20% cells with 9p21 homozygous loss)	Unclear, diagnostic accuracy only assessed in 155/265 of patients	None reported
Ianari, 1997[17] Italy Moderate	13/75 (17%) Tumor stage: 18 Ta, 4 T1 and CIS, 13 T2, 4 T3, 1 T4, 3 CIS Tumor grade: 1 G1, 2 G2, 3 G3, 7 Gx	BTA stat: positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Halling, 2002[16] USA High	BTA stat Overall: 0.78 (56/72) Ta: 0.63 (24/38) T1-T4: 0.94 (16/17) CIS: 0.94 (16/17) G1: 0.50 (6/12) G2: 0.72 (18/25) G3: 0.91 (32/35) FISH (UroVysion) Overall: 0.81 (59/73) Ta: 0.65 (24/37) T1-T4: 0.95 (18/19) CIS: 1.0 (17/17) G1: 0.36 (4/11) G2: 0.76 (19/25) G3: 0.97 (36/37)	BTA stat Overall: 0.74 (59/80) FISH (UroVysion) Overall: 0.96 (75/78)	BTA stat Overall: 3.0 FISH (UroVysion) Overall: 20	BTA stat Overall: 0.30 FISH (UroVysion) Overall: 0.20
Ianari, 1997[17] Italy Moderate	Overall: 0.54 (7/13) G1: 0.00 (0/1) G2: 0.50 (1/2) G3: 1.00 (3/3) (excludes 7 cases with unknown grade)	Overall: 0.85 (53/62)	Overall: 3.6	Overall: 0.54

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Halling, 2002[16] USA High	BTA stat Overall: 0.73 (56/77) FISH (UroVysion) Overall: 0.95 (59/62)	BTA stat Overall: 0.79 (59/75) FISH (UroVysion) Overall: 0.84 (75/89)	Not reported	Not reported	265 patients evaluated, sensitivity evaluated in 75 patients with bladder cancer but specificity only evaluated in 80 patients without bladder cancer
Ianari, 1997[17] Italy Moderate	Overall: 0.44 (7/16)	Overall: 0.90 (53/59)	Not reported	Not reported, BTA tests provided by Bard Diagnostic Sciences	Reports specificity of 91% based on per-cystoscopy evaluation; results reported here as per patient

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Irani, 1999[18] France Moderate	BTA stat BTA TRAK	Prospective	Cystoscopy with pathological confirmation	Patients with or without a history of bladder cancer with symptoms suspicious for bladder cancer (n=81)	Mean age: Not reported Male: 83% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Karnwal, 2010[19] USA Moderate	FISH (UroVysion)	Retrospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for NMIBC (n=59)	Mean age: 56 years Male: 68% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 33 Ta, 22 T1, 2 T1 and CIS; 23 G1, 20 G2, 16 G3

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Irani, 1999[18] France Moderate	49/81 (60%) Tumor stage: 28 Ta, 11 T1, 10 ≥T2 Tumor grade: 19 G1, 18 G2, 12 G3	BTA stat: positive BTA TRAK: >14 U/m	Not reported	None reported
Karnwal, 2010[19] USA Moderate	48/59 (81%) Tumor grade: 23 G1 or G2, 25 G3	FISH: Positive (criteria not reported)	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Irani, 1999[18] France Moderate	BTA stat Overall: 0.65 (32/49) Ta: 0.50 (14/28) T1: 0.73 (8/11) ≥T2: 1.0 (10/10) G1: 0.53 (10/19) G2: 0.72 (13/18) G3: 0.92 (11/12) BTA TRAK Overall: 0.78 (38/49) Ta: 0.68 (19/28) T1: 0.82 (9/11) ≥T2: 1.0 (10/10) G1: 0.74 (14/19) G2: 0.72 (13/18) G3: 0.92 (11/12)	BTA stat Overall: 0.72 (23/32) BTA TRAK Overall: 0.62 (20/32)	BTA stat Overall: 2.3 BTA TRAK Overall: 2.1	BTA stat Overall: 0.49 BTA TRAK Overall: 0.35
Karnwal, 2010[19] USA Moderate	Overall: 0.62 (30/48)	Overall: 0.65 (30/46)	Overall: 1.8	Overall: 0.57

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Irani, 1999[18] France Moderate	BTA stat Overall: 0.78 (32/41) BTA TRAK Overall: 0.76 (38/50)	BTA stat Overall: 0.58 (23/40) BTA TRAK Overall: 0.65 (20/31)	Not reported	Not reported	
Karnwal, 2010[19] USA Moderate	Overall: 0.65 (30/46)	Overall: 0.63 (30/48)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Leyh, 1997a[20] Germany, UK, and France Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with (n=69) or without (n=345) a history of bladder cancer suspected of having bladder cancer based on signs, symptoms, recent intravenous urography, or recent cystoscopy	Mean age: 60 years Male: 64% Race: Not reported Smoker: Not reported Signs or symptoms (n=413): 122 gross hematuria, 323 microscopic hematuria, 75 dysuria, 148 bladder irritability, 77 urinary urgency, 39 flank pain, 44 suspicious cystoscopy, 21 abnormal intravenous urography Prior bladder cancer stage/grade: Not reported
Leyh, 1997b[21] Germany and France Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for treatment bladder cancer (n=164)	Mean age: 67 years Male: 77% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Leyh, 1997a[20] Germany, UK, and France Moderate	71/414 (17%) Tumor stage: 28 Ta, 23 T1, 18 ≥T2, 4 CIS Tumor grade: 6 G1, 36 G2, 25 G3	BTA stat: Positive	Not reported	None reported
Leyh, 1997b[21] Germany and France Moderate	39/164 (24%) Tumor stage: 15 Ta, 10 T1, 10 ≥T2 Tumor grade: 10 G1, 16 G2, 12 G3	BTA stat: Positive	Not reported	14 patients excluded from analysis with "suspicion" of bladder cancer but no confirmed diagnosis

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Leyh, 1997a[20] Germany, UK, and France Moderate	Overall: 0.70 (50/71) Ta: 0.38 (9/24) T1: 0.87 (20/23) ≥T2: 0.89 (16/18) G1: 0.17 (1/6) G2: 0.64 (23/36) G3: 0.92 (23/25) Primary: 0.80 (33/41) Recurrent: 0.57 (17/30)	Overall: 0.90 (304/337) Primary: 0.91 (277/304) Recurrent: 0.82 (27/33)	Overall: 7.0 Primary: 8.0 Recurrent: 3.2	Overall: 0.33 Primary: 0.21 Recurrent: 0.52
Leyh, 1997b[21] Germany and France Moderate	BTA STAT Overall: 0.54 (21/39) Ta: 0.33 (5/15) T1: 0.60 (6/10) ≥T2: 0.80 (8/10) G1: 0.30 (3/10) G2: 0.44 (7/16) G3: 0.92 (11/12) BTA STAT plus cytology Overall: 0.64 (25/39)	BTA STAT Overall: 0.92 (102/111) BTA STAT plus cytology Overall: Not reported	BTA STAT Overall: 6.8 BTA STAT plus cytology Overall: Not calculable	BTA STAT Overall: 0.50 BTA STAT plus cytology Overall: Not calculable

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Leyh, 1997a[20] Germany, UK, and France Moderate	Overall: 0.60 (50/83) Primary: 0.55 (33/60) Recurrent: 0.74 (17/23)	Overall: 0.94 (304/325) Primary: 0.97 (277/285) Recurrent: 0.68 (27/40)	Not reported	Bard Diagnostic Sciences	0.15 with suspicious cystoscopy or abnormal intravenous urography
Leyh, 1997b[21] Germany and France Moderate	BTA STAT Overall: 0.70 (21/30) BTA STAT plus cytology Overall: Not reported	BTA STAT Overall: 0.85 (102/120) BTA STAT plus cytology Overall: Not reported	Not reported	Bard Diagnostic Sciences	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Lodde, 2003[22] Italy Moderate	uCyt+	Prospective	Cystoscopy with pathological confirmation	Patients with signs and symptoms suspicious for bladder cancer (e.g., microhematuria or gross hematuria and/or irritative symptoms) (n=98) or surveillance after TURBT (n=137)	Mean age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Lodde, 2003[22] Italy Moderate	51/91 (56%) primary Tumor stage: 29 Ta, 13 T1, 6 ≥T2, 3 CIS Tumor grade: 20 G1, 18 G2, 13 G3 51/134 (38%) recurrent Tumor stage: 33 Ta, 3 t1, 5 ≥T2, 10 CIS Tumor grade: 23 G1, 10 G2, 18 G3	uCyt+: Positive	10 patients had too few cells for uCyt+	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Lodde, 2003[22] Italy Moderate	Overall: 0.87 (89/102) Ta: 0.81 (50/62) T1: 0.94 (15/16) ≥T2: 0.91 (10/11) CIS: 1.0 (13/13) G1: 0.81 (35/43) G2: 0.89 (25/28) G3: 0.94 (29/31) Primary: 0.92 (47/51) Ta: 0.86 (25/29) T1: 1.00 (13/13) ≥T2: 0.83 (5/6) CIS: 1.00 (3/3) G1: 0.85 (17/20) G2: 1.00 (18/18) G3: 0.92 (12/13) Recurrent: 0.82 (42/51) Ta: 0.76 (25/33) T1: 0.67 (2/3) ≥T2: 1.00 (5/5) CIS: 1.00 (10/10) G1: 0.78 (18/23) G2: 0.70 (7/10) G3: 0.94 (17/18)	Overall: 0.67 (83/123) Primary: 0.75 (30/40) Recurrent: 0.64 (53/83)	Overall: 2.6 Primary: 3.7 Recurrent: 2.3	Overall: 0.19 Primary: 0.11 Recurrent: 0.28

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Lodde, 2003[22] Italy Moderate	Overall: 0.69 (89/129) Primary: 0.82 (47/57) Recurrent: 0.53 (42/79)	Overall: 0.86 (83/96) Primary: 0.88 (30/34) Recurrent: 0.90 (53/59)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Messing, 2005[23] USA Moderate	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for completed resected stage T1 or less urothelial cancer, focus on grade 1 and 2 cancer (n=327)	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: All T1 or less; no other data provided

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Messing, 2005[23] USA Moderate	61/327 (19%) Tumor stage: 35 Ta, 8 T1, 2 T2, 5 CIS, 9 Tx Tumor grade: 28 G1, 10 G2, 6 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	14 patients had too few cells for ImmunoCyt	9 patients had cystoscopically evident tumors that were fulgurated, with no tissue for histology

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Messing, 2005[23] USA Moderate	ImmunoCyt Overall: 0.81 (42/52) Ta: 0.83 (29/35) T1: 0.75 (6/8) T2: 1.00 (2/2) CIS: 1.00 (5/5) G1: 0.79 (22/28) G2: 0.90 (9/10) G3: 0.67 (4/6) ImmunoCyt + cytology Overall: 0.81 (42/52) Ta: 0.83 (29/35) T1: 0.75 (6/8) T2: 1.00 (2/2) CIS: 1.00 (5/5) G1: 0.79 (22/28) G2: 0.90 (9/10) G3: 0.67 (4/6)	ImmunoCyt Overall: 0.75 (206/274) ImmunoCyt + cytology: Overall: 0.73 (201/274)	ImmunoCyt Overall: 3.2 ImmunoCyt + cytology Overall: 3.0	ImmunoCyt Overall: 0.25 ImmunoCyt + cytology Overall: 0.26

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Messing, 2005[23] USA Moderate	ImmunoCyt Overall: 0.38 (42/110) ImmunoCyt + cytology Overall: 0.37 (42/115)	ImmunoCyt Overall: 0.95 (206/216) ImmunoCyt + cytology Overall: 0.95 (206/216)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Mian, 1999[24] Italy Moderate	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance (n=142) or with signs and symptoms (n=107)	Mean age: 66 years Male: 77% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Mian, 2000[25] Italy and Austria Moderate	BTA stat	Retrospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=57) or undergoing surveillance for bladder cancer (n=123)	Mean age: 66 years Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Mian, 1999[24] Italy Moderate	56/142 (39%) primary, 23/107 (21%) recurrent Tumor stage: 43 Ta, 20 T1, 12 ≥T2, 4 CIS Tumor grade: 25 G1, 25 G2, 29 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	15 had fewer than 500 cells/slide	None reported
Mian, 2000[25] Italy and Austria Moderate	53/180 (29%) Tumor stage: 28 Ta, 13 T1, 7 ≥T2, 1 CIS Tumor grade: 18 G1, 19 G2, 16 G3	BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Mian, 1999[24] Italy Moderate	ImmunoCyt Overall: 0.86 (68/79) Ta: 0.86 (37/43) T1: 0.85 (17/20) ≥T2: 0.83 (10/12) CIS: 1.0 (4/4) G1: 0.84 (21/25) G2: 0.84 (21/25) G3: 0.90 (26/29) Primary: 0.91 (21/23) Recurrent: 0.84 (47/56) ImmunoCyt + cytology Overall: 0.90 (71/79) Ta: 0.88 (38/43) T1: 0.90 (18/20) ≥T2: 0.92 (11/12) CIS: 1.0 (4/4) G1: 0.84 (21/25) G2: 0.88 (22/25) G3: 0.97 (28/29) Primary: 0.96 (22/23) Recurrent: 0.88 (49/56)	ImmunoCyt Overall: 0.79 (135/170) Primary: 0.79 (66/84) Cystitis: 0.60 (6/10) Urolithiasis: 0.92 (22/24) Benign lower urinary tract lesion: 0.50 (8/16) Microhematuria: 0.85 (23/27) Renal, prostate, or cervical cancer: 1.0 (7/7) Recurrent: 0.80 (69/86) ImmunoCyt + cytology Overall: 0.79 (135/170) Primary: 0.79 (66/84) Cystitis: 0.60 (6/10) Urolithiasis: 0.92 (22/24) Benign lower urinary tract lesion: 0.50 (8/16) Microhematuria: 0.85 (23/27) Renal, prostate, or cervical cancer: 1.0 (7/7) Recurrent: 0.80 (69/86)	ImmunoCyt Overall: 4.1 Primary: 4.3 Recurrent: 4.2 ImmunoCyt + cytology Overall: 4.3 Primary: 4.6 Recurrent: 4.4	ImmunoCyt Overall: 0.18 Primary: 0.11 Recurrent: 0.20 ImmunoCyt + cytology Overall: 0.13 Primary: 0.05 Recurrent: 0.15
Mian, 2000[25] Italy and Austria Moderate	Overall: 0.53 (28/53) Ta: 0.43 (12/28) T1: 0.62 (8/13) ≥T2: 0.70 (7/10) CIS: 0.50 (1/2) G1: 0.39 (7/18) G2: 0.53 (10/19) G3: 0.69 (11/16)	Overall: 0.70 (89/127)	Overall: 1.8	Overall: 0.67

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Mian, 1999[24] Italy Moderate	ImmunoCyt Overall: 0.66 (68/103) Primary: 0.54 (21/39) Recurrent: 0.73 (47/64) ImmunoCyt + cytology Overall: 0.67 (71/106) Primary: 0.55 (22/40) Recurrent: 0.74 (49/66)	ImmunoCyt Overall: 0.92 (135/146) Primary: 0.97 (66/68) Recurrent: 0.88 (69/78) ImmunoCyt + cytology Overall: 0.94 (135/143) Primary: 0.99 (66/67) Recurrent: 0.91 (69/76)	Not reported	DiagnoCure, Inc.	
Mian, 2000[25] Italy and Austria Moderate	Overall: 0.42 (28/66)	Overall: 0.78 (89/114)	Not reported	Not reported	Studies reports PPV of 0.43 and 0.79, results reported here are based on 2 x 2 tables

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Nasuti, 1999[26] USA Moderate	BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with dysuria, incontinence, gross hematuria, or microscopic hematuria (n=100)	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Nasuti, 1999[26] USA Moderate	3/100 (3%) Tumor stage: 2 noninvasive, 1 invasive Tumor grade: 2 G2, 1 G3	BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as **n/N**	Specificity-Report as **n/N**	Positive Likelihood Ratio	Negative Likelihood Ratio
Nasuti, 1999[26] USA Moderate	1.0(3/3)	0.84 (81/97)	6.2	0

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Nasuti, 1999[26] USA Moderate	0.16 (3/19)	1.0 (81/81)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
O'Sullivan, 2012[27] New Zealand Moderate	Cxbladder NMP22 (qualitative, Bladderchek) NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with recent gross hematuria, no prior history of bladder cancer (n=485)	Median age: 69 years Male: 80% Race: 87% European, 6.8% Maori Smoker: 16% current, 44% ex-smoker, 40% never smoker Signs or symptoms: 100% gross hematuria

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
O'Sullivan, 2012[27] New Zealand Moderate	66/485 (14%) Tumor stage: 38 Ta, 16 T1, 9 T2, 2 ≥T3, 2 CIS Tumor grade: 3 G1, 38 G2, 24, G3 (WHO 1973); 32 low, 4 mixed, 29 high (WHO ISUP 1998)	Cxbladder: At values giving 85% or 90% specificity NMP22 qualitative (Bladderchek): positive NMP22 quantitaive: >7.5 U/ml	1 patient Bladderchek failed; 3 missing uRNA	9 patients did not have cystoscopy performed, 1 missing cytology

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
O'Sullivan, 2012[27] New Zealand Moderate	Cxbladder (85% specificity) Overall: 0.82 (54/66) Ta: 0.68 (25/37) T1: 1.0 (16/16) T2: 1.0 (9/9) ≥T3: 1.0 (2/2) CIS: 1.0 (2/2) G1: 0.33 (1/3) G2: 0.76 (29/38) G3: 0.96 (23/24) Unifocal: 0.79 (41/52) Multifocal: 0.92 (12/13) Male: 0.80 (49/61) Female: 1.0 (5/5) Cxbladder (95% specificity) Overall: 0.73 (48/66) NMP22 >7.5 U/ml Overall: 0.50 (33/66) Ta: 0.35 (13/37) T1: 0.75 (12/16) T2: 0.67 (6/9) ≥T3: 1.0 (2/2) CIS: 0 (0/2) G1: 0.33 (1/3) G2: 0.39 (15/38) G3: 0.71 (17/24) Unifocal: 0.44 (23/52) Multifocal: 0.77 (10/13) Male: 0.48 (29/61)	Cxbladder (85% specificity) Overall: 0.85 (357/419) No diagnosis: 0.88 (144/164) BPH/prostatitis: 0.85 (110/130) UTI or inflammation of urinary tract: 0.82 (32/39) Calculi: 0.68 (19/28) Hematuria due to warfarin: 0.80 (8/10) Other urological cancer: 0.80 (4/5) Cxbladder (95% specificity) Overall: 0.90 (377/419) NMP22 >7.5 U/ml Overall: 0.88 (369/419) No diagnosis: 0.88 (144/164) BPH/prostatitis: 0.90 (117/130) UTI or inflammation of urinary tract: 0.87 (34/39) Calculi: 0.82 (23/28) Hematuria due to warfarin: 0.90 (9/10) Other urological cancer: 0.80 (4/5) NMP22 Bladderchek Overall: 0.96 (404/419) No diagnosis: 0.98 (161/164)	Cxbladder (85% specificity) Overall: 0.47 (54/116) Cxbladder (95% specificity) Overall: 0.53 (48/90) NMP22 >7.5 U/ml Overall: 0.40 (33/83) NMP22 Bladderchek Overall: 0.62 (25/40)	Cxbladder (85% specificity) Overall: 0.97 (357/369) Cxbladder (95% specificity) Overall: 0.95 (377/395) NMP22 >7.5 U/ml Overall: 0.92 (369/402) NMP22 Bladderchek Overall: 0.91 (404/445)

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
O'Sullivan, 2012[27] New Zealand Moderate	Cxbladder (85% specificity) Overall: 5.5 Cxbladder (95% specificity) Overall: 7.3 NMP22 >7.5 U/ml Overall: 4.2 NMP22 Bladderchek Overall: 9.5	Cxbladder (85% specificity) Overall: 0.21 Cxbladder (95% specificity) Overall: 0.30 NMP22 >7.5 U/ml Overall: 0.23 NMP22 Bladderchek Overall: 0.65	Cxbladder: 0.87 (CI not reported) NMP22 ELISA: 0.73 NMP22 Bladderchek: Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
O'Sullivan, 2012[27] New Zealand Moderate (Continued)					
Paoluzzi, 1999[28] Italy Moderate	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients with gross or microscopic hematuria (n=90)	Age: Not reported Male: 85% Race: Not reported Smoker: Not reported Signs or symptoms: 100% gross or microscopic hematuria

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
O'Sullivan, 2012[27] New Zealand Moderate (Continued)				
Paoluzzi, 1999[28] Italy Moderate	32/90 (36%) Tumor stage: Not reported Tumor grade: Not reported	NMP22 quantitative: >10 u/ml	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
O'Sullivan, 2012[27] New Zealand Moderate (Continued)	NMP22 >7.5 U/ml (continued) Female: 0.80 (4/5) NMP22 Bladderchek Overall: 0.38 (25/66) Ta: 0.38 (14/37) T1: 0.50 (8/16) T2: 0.22 (2/9) ≥T3: 0.50 (1/2) CIS: 0 (0/2) G1: 0.33 (1/3) G2: 0.34 (13/38) G3: 0.46 (11/24) Unifocal: 0.33 (17/52) Multifocal: 0.62 (8/13) Male: 0.38 (23/61) Female: 0.40 (2/5)			
Paoluzzi, 1999[28] Italy Moderate	NMP22: 0.84 (27/32) NMP22 + cytology: 0.91 (29/32)	NMP22: 0.62 (36/58) NMP22 + cytology: 0.83 (48/58)	NMP22: 2.2 NMP22 + cytology: 5.4	NMP22: 0.26 NMP22 + cytology: 0.11

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
O'Sullivan, 2012[27] New Zealand Moderate (Continued)					
Paoluzzi, 1999[28] Italy Moderate	NMP22: 0.55 (27/49) NMP22 + cytology: 0.74 (29/39)	NMP: 0.88 (36/41) NMP + cytology: 0.94 (48/51)	Not reported	Not reported	Discrepancies between reported PPV of 0.30 and NPV of 0.40 and calculated 0.55 and 0.88 based on 2 x 2 table

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Pfister, 2003[29] France Moderate	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=236) or undergoing surveillance after TURBT for bladder cancer (n=458)	Mean age: 66 years Male: 79% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Pfister, 2003[29] France Moderate	57/236 (24%) primary; 85/458 (19%) recurrent Tumor stage: 75 Ta, 28 T1, 28 T2 or greater, 8 CIS Tumor grade: 31 G1, 40 G2, 68 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	14 patients ImmunoCyt not performed	52 patients did not have cystoscopy performed, 8 missing clinical pathology data

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Pfister, 2003[29] France Moderate	ImmunoCyt Overall: Not reported Ta: 0.70 T1: 0.67 T2: 0.73 CIS: 1.00 G1: 0.61 G2: 0.76 G3: 0.77 Primary: 0.73 Recurrent: 0.70 ImmunoCyt + cytology Overall: Not reported Ta: 0.75 T1: 0.78 T2: 0.91 CIS: 1.00 G1: 0.67 G2: 0.78 G3: 0.87 Primary: 0.84 Recurrent: 0.76	ImmunoCyt Overall: Not reported Ta: 0.75 T1: 0.78 T2: 0.91 CIS: 1.00 G1: 0.67 G2: 0.78 G3: 0.87 Primary: 0.85 (144/170) Recurrent: 0.84 (302/360) ImmunoCyt + cytology Primary: 0.82 Recurrent: Not reported	ImmunoCyt Primary: 4.9 Recurrent: 4.4 ImmunoCyt + cytology Primary:4.7 Recurrent: Not calculable	ImmunoCyt Primary: 0.32 Recurrent: 0.36 ImmunoCyt + cytology Primary: 0.20 Recurrent: Not calculable

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Pfister, 2003[29] France Moderate	Not reported	Not reported	Not reported	Ferring Laboratories provided ImmunoCyt tests; otherwise not reported	Discrepancies in reported true negatives; discrepancies between reported sensitivities and calculated 2 x 2 tables and unable to calculate most n/N

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Placer, 2002[30] Spain Moderate	FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=34), with symptoms suggestive of bladder cancer (n=42), or undergoing transurethral resection of prostate (n=10)	Mean age: 70 years Male: 88% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Pode, 1999[31] Israel Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms of bladder cancer (n=88) or undergoing surveillance for bladder cancer (n=162)	Mean age: Not reported Male: 83% Race: Not reported Smoker: Not reported Signs or symptoms of bladder cancer: 88 with hematuria or irritative voiding symptoms, otherwise not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Placer, 2002[30] Spain Moderate	47/86 (55%) Tumor stage: 26 Ta, 12 T1, 9 T2-T4 Tumor grade: 16 G1, 12 G2, 19 G3	FISH: Positive (five or more cells with polysomy, or >50% of cells with loss of two 9p21 signals)	FISH not interpretable in 6 patients	None reported
Pode, 1999[31] Israel Moderate	71/88 (81%) primary; 57/162 (35%) recurrent Tumor stage: 72 Ta, 29 T1, 13 T2 or T3a, 14 T3b or higher Tumor grade: 25 G1, 58 G2, 45 G3	BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Placer, 2002[30] Spain Moderate	FISH (UroVysion) Overall: 0.80 (37/46) Ta: 0.64 (16/25) T1: 1.0 (12/12) T2- T4: 1.0 (9/9) G1: 0.53 (8/15) G2: 0.83 (10/12) G3: 1.0 (19/19) Primary: 0.86 (25/2 9) Recurrent: 0.71 (12/17) <10 mm: 0.46 (6/13) 10-30 mm: 0.93 (14/15) >30 mm: 0.94 (17/18) FiSH (UroVysion) + cytology Overall: 0.83 (38/46)	FISH (UroVysion) Overall: 0.85 (29/34) Primary: 1.0 Recurrent: 0.88 FISH (UroVysion) + cytology Overall: 0.79 (27/34)	FISH (UroVysion) Overall: 5.3 Primary: Not calculable Recurrent: 5.9	FISH (UroVysion) Overall: 0.24 Primary: 0.14 Recurrent: 0.33
Pode, 1999[31] Israel Moderate	Overall: 0.83 (106/128) <2 cm: 0.60 (32/53) 2-5 cm: 0.96 (53/55) >5: 1.0 (20/20) G1: 0.40 (10/25) G2: 0.84 (49/58) G3: 1.0 (45/45) Ta: 0.72 (52/72) T1: 0.90 (26/29) T2 or T3a: 1.0 (13/13) T3b or higher: 1.0 (14/14) Primary: 0.90 (64/71) Recurrent: 0.74 (42/57)	Overall: 0.69 (84/122) Primary: 0.76 (13/17) Recurrent: 0.68 (71/105)	Overall: 2.7 Primary: 3.8 Recurrent: 2.3	Overall: 0.25 Primary: 0.13 Recurrent: 0.38

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Placer, 2002[30] Spain Moderate	FISH (UroVysion) Overall: 0.88 (37/42)	FISH (UroVysion) Overall: 0.76 (29/38)	Not reported	Spanish Urological Association	Unable to calculate n/N for specificity stratified according to primary and recurrent tumors
Pode, 1999[31] Israel Moderate	Overall: 0.74 (106/144) Primary: 0.94 (64/68) Recurrent: 0.55 (42/76)	Overall: 0.79 (84/106) Primary: 0.65 (13/20) Recurrent: 0.83 (71/86)	Not reported	Not reported	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Ponsky, 2001[32] USA Moderate	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=529) or undergoing surveillance for bladder cancer (n=79)	Mean age: 70 years in patients with cancer 61 years in patients without cancer 72% male Race: Not reported Smoker: Not reported Signs or symptoms: 143 gross hematuria, 226 microscopic hematuria, 239 urinary frequency or dysuria Prior bladder cancer stage: Not reported
Quek, 2002[33] Singapore Moderate	BTA stat	Prospective	Cystoscopy and intravenous urogram with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=106) or undergoing surveillance for bladder cancer (n=13)	Mean age: 54 years 68% male Race: Not reported Smoker: Not reported Signs or symptoms: 60 gross hematuria, 29 microhematuria, 13 vesical irritability Prior bladder cancer stage: Not reported
Raitanen, 2001[34] Finland Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation, urography or renal ultrasound if positive BTA stat and negative cystoscopy	Patient undergoing surveillance for bladder cancer (n=501)	Mean age: 69 years 79% male Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 242 Ta, 187 T1, 20 CIS, 52 Tx; 220 G1, 215 G2, 52 G3, 14 Gx

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Ponsky, 2001[32] USA Moderate	52/608 (8.6%) Tumor stage and grade: 30 Ta and grade 1 to 2, 12 T1 and grade 2 to 3, 7 T2 and grade 3 or greater, 3 Tis	NMP22: >10 u/ml	Not reported	None reported
Quek, 2002[33] Singapore Moderate	15% (16/106) primary; 31% (4/13) recurrent Tumor stage: 4 Ta, 10 T1, 6 T2-T4 Tumor grade: 7 G1, 6 G2, 7 G3	BTA stat: Positive	Not reported	None reported
Raitanen, 2001[34] Finland Moderate	131/501 (26%) Tumor stage: 56 Ta, 23 T1, 3 T2-3, 12 CIS, 37 Tx Tumor grade: 52 G1, 37 G2, 8 G3, 34 Gx	BTA stat: Positive	Not reported	55 did not undergo reference standard and other testing and excluded from analysis

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Ponsky, 2001[32] USA Moderate	0.88 (46/52)	0.84 (467/556)	5.5	0.14
Quek, 2002[33] Singapore Moderate	Overall: 0.85 (17/20) Ta: 0.25 (1/4) T1: 1.00 (10/10) T2- T4: 1.00 (6/6) G1: 0.57 (4/7) G2: 1.00 (6/6) G3: 1.00 (7/7)	Overall: 0.63 (62/99) Less than 40 years old: 0.78 (14/18) More than 40 years old: 0.59 (47/80)	2.3	0.24
Raitanen, 2001[34] Finland Moderate	Not reported	0.81 (254/315)	Not calculable	Not calculable

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Ponsky, 2001[32] USA Moderate	0.34 (46/135)	0.99 (467/473)	Not reported	Not reported	
Quek, 2002[33] Singapore Moderate	0.31 (17/54)	0.95 (62/65)	Not reported	Not reported	Specificity reported by presenting symptom but does not match data provided
Raitanen, 2001[34] Finland Moderate	Not reported	Not reported	Not reported	Tampere University Hospital	9/61 patients without bladder tumor on initial cystoscopy had bladder cancer at subsequent followup

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Saad, 2002[35] UK Moderate	NMP22 (quantitative) BTA stat	Prospective	Cystoscopy with pathological confirmation	Referred for evaluation of various urological conditions (n=120)	Mean age: 70 years Male: 83% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported
Sanchez-Carbayo, 2001[36] Spain Moderate	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with microscopic hematuria (n=112)	Mean age: 66 years 65% male Race: Not reported Smoker: Not reported Signs or symptoms: All had microscopic hematuria

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Saad, 2002[35] UK Moderate	52/73 (71%) with bladder cancer Tumor stage: 23 Ta, 20 T1, 8 T2, 6 CIS Tumor grade: 13 G1, 22 G2, 17 G3	NMP22 quantitative: ≥10 u/ml BTA stat: Positive	Not reported	None reported
Sanchez-Carbayo, 2001[36] Spain Moderate	43/112 (38%) Tumor stage: 5 Ta, 28 T1, 7 T2, 2 T3, 1 CIS Tumor grade: 11 G1, 15 G2, 17 G3	NMP22 quantitative: >10 u/ml	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Saad, 2002[35] UK Moderate	BTA stat Overall: 0.63 (33/52) Ta: 0.48 (11/23) T1: 0.80 (16/20) T2: 1.0 (8/8) CIS: 1.0 (6/6) G1: 0.23 (3/13) G2: 0.68 (15/22) G3: 0.88 (15/17) NMP22 Overall: 0.81 (42/52) Ta: 0.70 (16/23) T1: 0.90 (18/20) T2: 1.0 (8/8) CIS: 1.0 (6/6) G1: 0.62 (8/13) G2: 0.86 (19/22) G3: 0.88 (15/17)	BTA stat Overall: 0.82 (56/68) NMP22 Overall: 0.87 (59/68)	BTA stat Overall: 3.5 NMP22 Overall: 6.2	BTA stat Overall: 0.45 NMP22 Overall: 0.22
Sanchez-Carbayo, 2001[36] Spain Moderate	Overall: 0.58 (25/43) T1: 0.57 (16/28) T2: 0.86 (6/7) T3: 1.00 (2/2) CIS: 0.0 (0/1) G1: 0.18 (2/11) G2: 0.60 (9/15) G3: 0.82 (14/17)	Overall: 0.90 (62/69)	Overall: 5.8	Overall: 0.47

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Saad, 2002[35] UK Moderate	BTA stat Overall: 0.73 (33/45) NMP22 Overall: 0.82 (42/51)	BTA stat Overall: 0.75 (56/75) NMP22 Overall: 0.86 (59/69)	Not reported	Not reported	
Sanchez-Carbayo, 2001[36] Spain Moderate	Overall: 0.78 (25/32)	Overall: 0.78 (62/80)	Not reported	IDL and Roche Diagnostics supplied materials, otherwise not reported	Discrepancies between reported measures for diagnostic accuracy and calculated measures from 2 x 2 tables based on data provided; number of cancers 25 when reported by tumor grade and 24 when reported by tumor stage; results based on accuracy reported by tumor grade

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Sarosdy, 2002[37] USA Moderate	FISH (UroVysion) BTA stat	Prospective	Cystoscopy with pathological confirmation or underwent ablation	Patients undergoing surveillance for bladder cancer (n=176)	Mean age: 71 years 75% male Non-white race: 13% Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 118 Ta, 20 T1, 4 T2, 29 CIS, 5 Tx; 70 G1, 56 G2, 46 G3, 4 Gx
Sawczuk, 2000[38] USA Moderate	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=56)	Mean age: 69 years Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 35 Ta, 14 T1, 2 T2, 5 T3-4; 31 G1 or G2, 25 G3 or G4 (7 with associated CIS)

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Sarosdy, 2002[37] USA Moderate	62/176 (35%) Tumor stage: 32 Ta, 6 T1, 3 T2, 7 CIS, 11 Tx Tumor grade: 22 G1, 9 G2, 18 G3	FISH: Positive (Criteria not reported) BTA stat: Positive	Unclear	Unclear (58 excluded due to no specimen, insufficient urine volume, suspicious cystoscopy but no pathology)
Sawczuk, 2000[38] USA Moderate	34/56 (61%) Tumor stage: 27 Ta, 4 T1, 3 T3b or 4 Tumor grade: 22 G1-2, 12 G3-4	NMP quantitative: >10 u/ml	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Sarosdy, 2002[37] USA Moderate	FISH (UroVysion) Overall: 0.71 (44/62) Ta: 0.66 (21/32) T1: 0.83 (5/6) T2: 1.0 (3/3) CIS: 1.0 (7/7) G1: 0.55 (12/22) G2: 0.78 (7/9) G3: 1.0 (7/7) Prior BCG: 0.85 (22/26) BTA stat Overall: Not reported Ta: 0.50 (16/32) T1: 0.83 (5/6) T2: 0.67 (2/3) CIS: 0.43 (3/7) G1: 0.27 (6/22) G2: 0.78 (7/9) G3: 0.72 (13/18) Prior BCG: 0.69 (18/26)	FISH (UroVysion) Overall: 0.66 (75/114) Prior BCG: 0.70 (38/54) BTA stat Overall: Not reported Prior BCG: 0.55 (30/55)	FISH (UroVysion) Overall: 2.1 Prior BCG: 2.8 BTA stat Overall: Not reported Prior BCG: 1.5	FISH (UroVysion) Overall: 0.44 Prior BCG: 0.21 BTA stat Overall: Not reported Prior BCG: 0.56
Sawczuk, 2000[38] USA Moderate	Overall: 0.62 (21/34) G1-2: 0.55 (12/22) G3-4: 0.75 (9/12)	Overall: 0.77 (17/22)	Overall: 2.7	Overall: 0.49

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Sarosdy, 2002[37] USA Moderate	FISH (UroVysion) Overall: 0.53 (44/83) Prior BCG: 0.58 (22/38) BTA stat Overall: Not reported Prior BCG: 0.42 (18/43)	FISH (UroVysion) Overall: 0.81 (75/93) Prior BCG: 0.90 (38/42) BTA stat Overall: Not reported Prior BCG: 0.79 (30/38)	Not reported	Not reported	
Sawczuk, 2000[38] USA Moderate	Overall: 0.81 (21/26)	Overall: 0.57 (17/30)	Not reported	Not reported	Study appeared to reverse PPV and NPV (Table 1).

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Schamhart, 1998[39] the Netherlands Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with history of bladder cancer undergoing surveillance or with symptoms suspicious for bladder cancer (n=149)	Mean age: 66 years 81% male Non-white race: 0% Smoker: Not reported Signs and symptoms: 10% gross hematuria, 4.7% microscopic hematuria, 0.5% flank pain, 2.6% dysuria, 4.7% dysuria, 2.6% urgency, 5.2% other symptoms Prior bladder cancer stage/grade: Not reported
Serretta, 1998[40] Italy Moderate	NMP22 (quantitative)	Unclear	Cystoscopy and intravenous urogram with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=137)	Mean age: 65 years Male: 89% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage and grade: 7 Tis, 49 Ta, 71 T1, 10 T2-3; 12 G1, 74 G2, 51 G3
Shariat, 2006[41] USA, Europe, Japan, Canada Moderate	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (Ta, T1, and/or Tis) (n=2,871)	Median age: 68 years Male: 76% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Schamhart, 1998[39] the Netherlands Moderate	62/149 (42%) Tumor stage: 42 Ta, 6 T1, 5 ≥T2, 3 CIS Tumor grade: 5 G1, 32 G2, 17 G3, 20 G3 + CIS	BTA stat: Positive	Unclear, 43 excluded for "protocol violations"	Unclear
Serretta, 1998[40] Italy Moderate	42/137 (31%) Tumor stage: Not reported Tumor grade: Not reported	NMP22 quantitative: >10 u/ml	Not reported	None reported
Shariat, 2006[41] USA, Europe, Japan, Canada Moderate	1045/2871 (36%) Tumor stage: 448 Ta, 276 T1, 220 ≥T2 Tumor grade: 233 G1, 420 G2, 329 G3	NMP22 quantitative: >10 u/ml; also various cutoffs from 1 to 30 u/ml	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Schamhart, 1998[39] the Netherlands Moderate	Overall: 0.32 (20/62) Ta: 0.24 (10/42) T1: 0.33 (2/6) ≥T2: 1.0 (5/5) CIS: 0.0 (0/3) G1: 0.60 (3/5) G2: 0.22 (7/32) G3 (no Tis): 0.41 (7/17) G3 + Tis: 0.35 (7/20) Low risk (TaG1/TaG2): 0.27 (9/33) High risk (TaG3/T1G2/T1G3/≥T2/Tis): 0.35 (8/23)	Overall: 0.82 (71/87)	Overall: 1.8	Overall: 0.83
Serretta, 1998[40] Italy Moderate	Overall: 0.72 (30/42)	Overall: 0.61 (58/95) Prior intravesical chemotherapy: 0.56 (27/48) No prior intravesical chemotherapy: 0.66 (31/47)	Overall: 1.8	Overall: 0.46
Shariat, 2006[41] USA, Europe, Japan, Canada Moderate	Overall: 0.57 (596/1045) ≥T2: 0.83 (183/220) G3: 0.75 (247/329) NMP >2, >6.5, >15, >20, >25, >30: 0.90 (940/1045), 0.68 (711/1045), 0.48 (502/1045), 0.42 (439/1045), 0.38 (397/1045), 0.36 (376/1045)	Overall: 0.81 (1479/1826) NMP >2, >6.5, >15, >20, >25, >30: 0.26 (475/1826), 0.67 (1223/1826), 0.88 (1607/1826), 0.92 (1680/1826), 0.94 (1716/1826), 0.95 (1735/1826)	Overall: 3.0 NMP >2, >6.5, >15, >20, >25, >30: 1.2, 2.1, 4.0, 5.2, 6.3, 7.2	Overall: 0.53 NMP >2, >6.5, >15, >20, >25, >30: 0.38, 0.48, 0.59, 0.63, 0.66, 0.67

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Schamhart, 1998[39] the Netherlands Moderate	Overall: 0.56 (20/36)	Overall: 0.63 (71/113)	Not reported	Test supplied by Bard Diagnostics; otherwise not reported	
Serretta, 1998[40] Italy Moderate	Overall: 0.45 (30/67)	Overall: 0.83 (58/70)	Not reported	Not reported	
Shariat, 2006[41] USA, Europe, Japan, Canada Moderate	Overall: 0.63 (596/943) NMP >2, >6.5, >15, >20, >25, >30: 0.41 (940/2291), 0.54 (711/1314), 0.70 (502/721), 0.75 (439/585), 0.78 (397/507), 0.81 (376/467)	Overall: 0.77 (1479/1928) NMP >2, >6.5, >15, >20, >25, >30: 0.82 (475/580), 0.79 (1223/1557), 0.75 (1607/2150), 0.73 (1680/2295), 0.73 (1716/2364), 0.72 (1735/2404)	Overall: 0.74 (95% CI 0.72 to 0.76)	Not reported	AUC for G3 vs. G1/2 or no cancer 0.81 (95% CI 0.78 to 0.83) AUC for ≥T2 vs. <T2 or no cancer 0.86 (95% CI 0.84 to 0.89)

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Sharma, 1999[42] USA Moderate	NMP22 (quantitative) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with symptoms of bladder cancer (n=278); 199 without prior cancer and 79 with prior cancer	Mean age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: 40% microscopic hematuria, 28% gross hematuria, 32% chronic irritative voiding symptoms Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Sharma, 1999[42] USA Moderate	34/278 (12%) with bladder cancer; 6/199 (3.0%) in persons without prior bladder cancer; 28/79 (35%) in persons with prior cancer Tumor stage: Not reported Tumor grade: Not reported	BTA stat: Positive NMP22 quantitative: >10 u/ml for primary, >6 u/ml for recurrent	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Sharma, 1999[42] USA Moderate	BTA stat Overall: 0.68 (23/34) Primary: 0.67 (4/6) Recurrent: 0.68 (19/28) NMP22 Overall: 0.82 (28/34) Primary: 0.67 (4/6) Recurrent: 0.86 (24/28)	BTA stat Overall: 0.82 (201/244) Primary: 0.82 Recurrent: 0.82 Benign inflammatory: 0.75 (47/63) Renal/bladder calculi: 0.57 (4/7) Foreign body: 0 (0/2) Bowel interposition segment: 0 (0/8) Other genitourinary cancer: 0.92 (54/59) Instrumentation: 0.60 (9/15) NMP22 Overall: 0.82 (200/244) Primary: 0.86 Recurrent: 0.67 Benign inflammatory: 0.78 (40/51) Renal/bladder calculi: 0.67 (4/6) Foreign body: 0 (0/2) Bowel interposition segment: 0 (0/6) Other genitourinary cancer: 0.82 (40/49) Instrumentation: 0.75 (9/12)	BTA stat Overall: 3.8 Primary: 3.7 Recurrent: 3.8 NMP22 Overall: 4.6 Primary: 4.8 Recurrent: 2.6	BTA stat Overall: 0.39 Primary: 0.40 Recurrent: 0.39 NMP22 Overall: 0.22 Primary: 0.38 Recurrent: 0.21

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Sharma, 1999[42] USA Moderate	BTA stat Overall: 0.35 (23/66) Primary: 0.68 Recurrent: 0.10 NMP22 Overall: 0.39 (28/72) Primary: 0.58 Recurrent: 0.13	BTA stat Overall: 0.95 (201/212) Primary: 0.82 Recurrent: 0.99 NMP22 Overall: 0.97 (200/206) Primary: 0.90 Recurrent: 0.99	Not reported	Not reported	Unable to calculate n/N for specificity or generate 2 x 2 table

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Thomas, 1999[43] Europe Moderate	BTA TRAK	Prospective	Cystoscopy with pathological confirmation	Patients with signs, symptoms, or imaging or cystoscopic findings suggestive of bladder cancer (n=96) or undergoing surveillance for bladder cancer (n=124)	Mean age: 64 years Male: 70% Caucasian: 98% Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[4] [4] UK Moderate	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=272) Excluded urinary infection or gross hematuria	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
van Der Poel, 1998[45] the Netherlands Moderate	BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=88) or undergoing cystoscopy with no prior bladder cancer (n=50) Excluded urinary tract infection	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Thomas, 1999[43] Europe Moderate	100/220 (45%) overall; 49/96 (51%) primary; 51/124 (41%) recurrent Tumor stage: 55 Ta, 24 T1, 16 T2- T4, 5 CIS Tumor grade: 25 G1, 41 G2, 34 G3	BTA TRAK: >14 kilounits/L	Not reported	None reported
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[4] [4] UK Moderate	102/272 (38%) Tumor stage: Not reported Tumor grade: Not reported	BTA stat: Positive	Not reported	None reported
van Der Poel, 1998[45] the Netherlands Moderate	58/103 (56%) Tumor stage: 40 Ta, 7 T1, 4 T2, 3 T3, 3 CIS Tumor grade: 7 G1, 27 G2, 20 G3	BTA stat: Positive	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Thomas, 1999[43] Europe Moderate	BTA TRAK Overall: 0.66 (66/100) Ta: 0.51 (28/55) T1: 0.88 (21/24) T2-T4: 0.88 (14/16) CIS: 0.60 (3/5) G1: 0.48 (12/25) G2: 0.59 (24/41) G3: 0.88 (30/34) Primary: 0.76 (37/49) Recurrent: 0.57 (29/51) BTA TRAK plus cytology (either positive) Overall: 0.71 (71/100)	BTA TRAK Overall: 0.69 (83/120) Primary: 0.53 (25/47) Primary, no GU disease: 0.64 (16/25) Primary, GU disease: 0.41 (9/22) Recurrent: 0.79 (58/73) Recurrent, no GU disease: 0.81 (52/64) Recurrent, GU disease: 0.48 (15/31) No GU disease: 0.76 (68/89) GU disease: 0.48 (15/31) BTA TRAK plus cytology (either positive) Overall: 0.69 (83/120)	BTA TRAK Overall: 2.1 BTA TRAK plus cytology Overall: 2.3	BTA TRAK Overall: 0.49 BTA TRAK plus cytology Overall: 0.20
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[4] [4] UK Moderate	0.58 (59/102)	0.85 (145/170)	3.7	0.53
van Der Poel, 1998[45] the Netherlands Moderate	Overall: 0.34 (20/58) Ta: 0.25 (10/40) T1: 0.57 (4/7) T2: 0.75 (3/4) T3: 1.0 (3/3) CIS: 0 (0/3) G1: 0.43 (3/7) G2: 0.33 (9/27) G3: 0.40 (8/20)	Overall: 0.81 (65/80)	Overall: 1.8	Overall: 0.81

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Thomas, 1999[43] Europe Moderate	BTA TRAK Overall: 0.64 (66/103) Primary: 0.63 (37/59) Recurrent: 0.66 (29/44) BTA TRAK plus cytology (either positive) Overall: 0.66 (71/108)	BTA TRAK Overall: 0.71 (83/117) Primary: 0.68 (25/37) Recurrent: 0.72 (58/80) BTA TRAK plus cytology (either positive) Overall: 0.74 (83/112)	Not reported	Bard Diagnostic Sciences	
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[4] [4] UK Moderate	0.70 (59/84)	0.77 (145/188)	Not reported	Bard UK Ltd.	Specificity reported as 86% but 85% based on 2 x 2 tables
van Der Poel, 1998[45] the Netherlands Moderate	Overall: 0.57 (20/35)	Overall: 0.63 (65/103)	Not reported	Bard Diagnostic Sciences	

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Varella-Garcia, 2004[46] USA Moderate	FISH (UroVysion)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=19)	Mean age: 69 years Male: 84% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported
Witjes, 1998[47] the Netherlands Moderate	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for NMIBC (n=50)	Age: Not reported Sex: Not reported Race: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: NMIBC, otherwise not reported
Zippe, 1999[48] USA Moderate	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients with microscopic or gross hematuria or other signs or symptoms suspicious for bladder cancer (n=146)	Mean age: 64 years Male: 77% Race: Not reported Smoker: Not reported Signs or symptoms: Not reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Varella-Garcia, 2004[46] USA Moderate	7/19 (37%) with bladder cancer Tumor stage: 3 Ta, 2 T1, 2 T2 Tumor grade: 2 G1, 3 G2, 2 G3	FISH: Positive (>16% cells with multiple chromosomes or >48% cells with 9p21 homozygous loss)	Not reported	None reported
Witjes, 1998[47] the Netherlands Moderate	12/50 (24%) with bladder cancer Tumor stage: 2 Ta, 1 T1, 3 T2, 1 Tis, 5 not available Tumor grade: 1 G1, 3 G2, 2 G3, 5 not available	NMP: >10 u/ml	Not reported	None reported
Zippe, 1999[48] USA Moderate	8/146 (5.5%) with bladder cancer Tumor stage: 3 Ta, 1 Ta/T1, 1 T1, 2 T2, 1 Tis Tumor grade: 2 G1, 1 G1/2, 2 G2, 1 G2/G3, 2 G3	NMP: >10 u/ml	Not reported	None reported

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Varella-Garcia, 2004[46] USA Moderate	Overall: 0.86 (6/7) Ta: 1.0 (3/3) T1: 0.50 (1/2) T2: 1.0 (2/2) G1: 1.0 (2/2) G2: 1.0 (3/3) G3: 0.50 (1/2)	Overall: 1.0 (12/12)	Overall: Not calculable (specificity 1.0)	Overall: 0.14
Witjes, 1998[47] the Netherlands Moderate	0.75 (9/12)	0.82 (31/38)	4.2	0.3
Zippe, 1999[48] USA Moderate	1.0 (8/8)	0.90 (124/138)	10	0

Appendix E1. Key Question 1: Diagnostic Accuracy

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Varella-Garcia, 2004[46] USA Moderate	Overall: 1.0 (6/6)	Overall: 0.92 (12/13)	Not reported	National Cancer Institute, Vysis Inc. provided UroVysion kit	
Witjes, 1998[47] the Netherlands Moderate	Overall: 0.56 (9/16)	Overall: 0.91 (31/34)	Not reported	Not reported	
Zippe, 1999[48] USA Moderate	0.36 (8/22)	1.0 (124/124)	Not reported	Not reported	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983 [50]) Medium	Japan Number sites: 33 Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Non-evaluated patients due to protocol violations, cessation of installation, adverse effects, or other reasons. Not quantified overall or by group.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	A vs. B vs. C vs. D Age (yrs), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: Not reported Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).	Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.05 Not reported for other treatment group comparisons. roup comparisons.	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.01 Comparisons not reported for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as non-significant, no p - values reported.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	A vs. B Recurrence-free survival rate at 540 days: 56.6% vs. 52.0%	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	Japan Number sites: Unclear Study years: July 1982 - 1985	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)	3.5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	A vs. B vs. C vs. D Age (yrs), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Sex (male): 80.1% (121/151) vs. 82.3% (130/158) vs. 82.0% (123/150) vs. 81.1% (120/148) Race: Not reported Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 31.8% (48/151) vs. 30.4% (48/158) vs. 36.0% (54/150) vs. 38.5% (57/148); 1-3 cm: 51.0% (77/151) vs. 53.2% (84/158) vs. 44.0% (66/150) vs. 49.3% (73/148); 3-5 cm: 14.6% (22/151) vs. 11.4% (18/158) vs. 11.3% (17/150) vs. 6.8% (10/148) Number of tumors: 1: 64.2% (97/151) vs. 55.7% (88/158) vs. 55.3% (83/150) vs. 66.9% (99/148); 2-4: 29.8% (45/151) vs. 30.4% (48/158) vs. 33.3% (50/150) vs. 23.6% (35/148); 5+: 6.0% (9/151) vs. 12.7% (20/158) vs. 10.7% (16/150) vs. 8.1% (12/148) * No data provided on stage or grade, but reported "absolutely no intergroup differences were found".	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0% vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1% vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, $p < 0.05$ B > D, $p < 0.05$ C > D, $p < 0.05$ Not reported for other treatment group comparisons.	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	A vs. B Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 Recurrence-free survival rate at 2 years: 62.3% vs. 59.1	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	Japan Number sites: Unclear Study years: July 1982 - May 1990	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)	Median, overall: 2,366 days (6.5 years); range: 480-2,817 days. Not reported for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: 671 Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: 134 Total Analyzed: 158 Per Group Analyzed: (44 vs. 42 vs. 41 vs. 31)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	Only reported overall; Not reported by treatment group Age ≤ 50 years: 13.3% (21/158) Age ≤ 60 years: 17.7% (28/158) Age < 70 years: 35.4% (56/158) Age ≥ 70 years: 33.5% (53/158) Sex (male): 84.8% (134/158) Race: NR Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: Tis: 1.3% (2/158); Ta: 44.3% (70/158); T1: 40.5% (64/158); Ta or T1: 13.9% (22/158) Grade: G1: 48.7% (77/158); G2: 45.6% (72/158); G1 or G2: 5.7% (9/158) Functional Status: NR	A vs. B vs. C vs. D Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31), "Statistics: no difference"	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	A vs. B Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42)	NR	NR	Ministry of Health and Welfare of Japan	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	Egypt Number sites: 1 Study years: January 1992 - February 1996	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages pTa or pT1, confirmed histologically; Grade G1 - G3. Multiplicity; Patients with pTa were included if they had multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function; CIS.	A: Epirubicin, 50 mg (in 50 ml normal saline); Single installation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 ml normal saline); Initial installation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, installations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.	16 to 49 months (mean 32.2, SD 11.4); Not reported for each group separately. Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years. Annual IVU. Urinalysis, urine culture, full blood count, and ECG before each installation.	Screened: 181 Randomized: 179 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 168 Per Group Analyzed (A vs. B vs. C): 55 vs. 59 vs. 54

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B vs. C Age, mean years (range): 52.1 (36-65) vs. 55 (30-68) vs. 53.4 (32-72) Race: NR Sex (male): 67.3% (37/55) vs. 74.6% (44/59) vs. 70.4% (38/54) Smoking status: NR Recurrent bladder cancer: 47.2% (26/55) vs. 52.5% (31/59) vs. 44.4% (24/54), p = 0.5 Stage: pTa: 16.3% (9/55) vs. 25.4% (15/59) vs. 18.5% (10/54); pT1: 83.7% (46/55) vs. 74.6% (44/59) vs. 81.5% (44/54), p = 0.4. Grade: G1: 10.9% (6/55) vs. 18.6% (11/59) vs. 25.9% (14/54); G2: 54.5% (30/55) vs. 55.9% (33/59) vs. 53.7% (29/54); G3: 34.5% (19/55) vs. 25.4% (15/59) vs. 20.4% (11/54), p = 0.2. Functional Status: NR Size: < 3 cm: 65% (36/55) vs. 71% (42/59) vs. 63% (34/54); ≥ 3 cm: 35% (19/55) vs. 29% (17/59) vs. 37% (20/54)	A vs. B vs. C Recurrence: 23.6% (13/55) vs. 25.4% (15/59) vs. 51.8% (28/54), A vs. B vs. C, p = 0.002, A and B vs. C, p < 0.001, A vs. B, p = 0.8. Mean interval to first recurrence, months: 16 vs. 18 vs. 6.9, p < 0.05. Recurrence rate per 100 patient-months: 0.79 vs. 0.84 vs. 2.01 Progression: 5.5% (3/55) vs. 3.4% (2/59) vs. 9.3% (5/54), p = 0.4.	A vs. B (No data for group C) Simple recurrence rate according to stage: Ta: 0.0% (0/9) vs. 0.0% (0/15); T1: 28.3% (13/46) vs. 34.1% (15/44), p = 0.7. Simple recurrence rate according to grade: G1: 0.0% (0/6) vs. 27.3% (3/11); G2: 10.0% (3/30) vs. 27.3% (9/33), p = 0.3; G3: 52.6% (10/19) vs. 20.0% (3/15), p = 0.05. Simple recurrence rate for large tumors (≥ 3 cm in greatest dimension): 21.1% (4/19) vs. 41.2% (7/17), p =0.5.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B Simple recurrence rate: 23.6% (13/55) vs. 25.4% (15/59), p = 0.8. Mean interval to first recurrence, months: 16 vs. 18 Recurrence rate per 100 patient-months: 0.79 vs. 0.84 Progression: 5.5% (3/55) vs. 3.4% (2/59)	NR	A vs. B (No data for group C) Proportion of patients with an adverse event: 21.8% (12/55) vs. 25.4% (15/59), p = 0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15) , p = 0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p = 0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.	No financial support received	Note: Possible overlap of some study subjects (group B) with those in Ali-El-Dein, 1997 (J Urol)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Ali-El-Dein, 1997[53] (J Urol) RCT Medium	Egypt Number sites: 1 Study years: June 1991 - May 1995	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function.	A: Epirubicin, 50 mg (in 50 ml normal saline). B: Epirubicin, 80 mg (in 50 ml normal saline). C: Doxorubicin, 50 mg (in 50 ml normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First installation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Installations once a week X 8 weeks, then once monthly to complete 1 year of treatment.	12 to 48 months (mean 30.1 months); Not reported for each group separately. Cysto-urethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter. Excretory urography every year. Urinalysis, urine culture, serum creatinine, CBC, ECG, and urine pH before and after each installation.	Screened: NR Randomized: 253 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 253 Per Group Analyzed (A vs. B vs. C vs. D): 64 vs. 68 vs. 60 vs. 61

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997[53] (J Urol) RCT Medium	A vs. B vs. C vs. D Age: NR Race: NR Sex (male): 81.4% (206/253), not reported by treatment group Smoking status: NR Recurrent bladder cancer: 37.5% (24/64) vs. 41.2% (28/68) vs. 43.3% (26/60) vs.45.9% (28/61) Stage: pTa: 10.9% (7/64) vs. 17.6% (12/68) vs. 6.7% (4/60) vs.9.8% (6/61); pT1: 89.1% (57/64) vs. 82.4% (56/68) vs. 93.3% (56/60) vs.90.2% (55/61); Tis associated: 6.3% (4/64) vs. 11.8% (8/68) vs. 0.0% (0/60) vs.0.0% (0/61) Grade: G1: 9.4% (6/64) vs. 16.2% (11/68) vs. 16.7% (10/60) vs.19.7% (12/61); G2: 78.1% (50/64) vs. 69.1% (47/68) vs. 70.0% (42/60) vs.65.6% (40/61); G3: 12.5% (8/64) vs. 14.7% (10/68) vs. 13.3% (8/60) vs.14.7% (9/61) Functional Status: NR	A vs. B vs. C vs. D Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61), A, B, and C vs. D, p = 0.0002, A and B vs. C, p = 0.02, A vs B, p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4); A, B, and C vs. D, p < 0.001; B vs. C, p = 0.05; A and B vs. C; p = 0.05. Recurrence rate per 100 patient-months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p < 0.001, A and B vs. C; p < 0.05, A vs. B, p < 0.05. Progression (to muscle invasive): 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), p = 0.6.	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 0.0% (0/16) vs. 0.0% (0/12) vs. 0.0% (0/22) vs. 2.5% (1/40), p > 0.05; T1: 93.8% (15/16) vs. 83.3% (10/12) vs. 100% (22/22) vs. 97.5% (39/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p = 0.01, A vs. B, p = NS; pTis: 6.3% (1/16) vs. 16.7% (2/12) vs. NA vs. NA. Simple recurrence rate according to grade: G1: 0.0% (0/16) vs. 16.7% (2/12) vs. 13.6% (3/22) vs. 12.5% (5/40), p > 0.05; G2: 75.0% (12/16) vs. 58.3% (7/12) vs. 68.2% (15/22) vs. 67.5% (27/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p = 0.04, A vs. B, p = NS; G3: 25.0% (4/16) vs. 25.0% (3/12) vs. 18.2% (4/22) vs. 20.0% (8/40), p > 0.05. Simple recurrence rate according to Grade 3-Stage pT1/Total: 66.7% (4/6) vs. 37.5% (3/8) vs. 57.1% (4/7) vs. 100% (8/8); A, B, and C vs. D, p < 0.05; A and B vs. C, p > 0.05.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997[53] (J Urol) RCT Medium	A vs. B Simple recurrence rate: 25.0% (16/64) vs. 17.6% (12/68), p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4). Recurrence rate per 100 patient-months: 0.83 vs. 0.60, p < 0.05. Progression: 10.9% (7/64) vs. 4.4% (3/68) Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44)	NR	A vs. B vs. C (No data for group D) Proportion of patients with an adverse event: 15.6% (10/64) vs. 23.5% (16/68) vs. 41.7% (25/60), A and B vs. C, p = 0.002, A vs. B, p = 0.3, B vs. C, p < 0.04. Adverse events per # of installations: 7.3% (88/1199) vs. 8.7% (111/1280) vs. 29.0% (324/1118), A and B vs. C, p < 0.0001, B vs. C, p < 0.05. Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) vs. 12.0% (3/25), p < 0.05 Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) vs. 60.0% (15/25), A and B vs. C, p = 0.02, A vs. B, p > 0.05, B vs. C, p = 0.3. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) vs. 12.0% (3/25), A and B vs. C, p > 0.05, A vs. B, p > 0.05, B vs. C, p > 0.05. Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) vs. 8.0% (2/25) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) vs. 4.0% (1/25) UTI: 10.0% (1/10) vs. 0.0% (0/16) vs. 4.0% (1/25)	NR	Note: Possible overlap of some study subjects (group A) with those in Ali-El-Dein, 1997 (British J Urol)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Berrum-Svennung, 2008[54] RCT Medium	Sweden Number sites: 13 September 1998 - September 2004	Non-muscle invasive papillary bladder tumor (primary or recurrent). Stage Ta or T1; Grade G1 or G2. Maximal tumor diameter 30 mm.	Intravesical treatment with BCG or chemotherapy in previous year; History of muscle-invasive tumor or grade G3 tumor; Stage T2.	A: Epirubicin, 50 mg (in 50 mL saline). Single installation within 6 hours after TURBT. Catheter clamped X 1 hour. B: Placebo. Saline, 50 mL. Single installation within 6 hours after TURBT. Catheter clamped X 1 hour.	2 years, overall; Not reported as median/mean, nor for each group. Evaluated with cystoscopy according to the routine at each study center. Study plan recommended cystoscopy every 4 months X 1 year, then every 6 months X 1 year. Participants were free to follow their respective clinical routines after installation.	Screened: NR Randomized: 404 (203 vs. 201) Postrandomization exclusions: 14 Lost to followup: 11 Total Analyzed: 307 Per Group Analyzed: (A vs. B): 155 vs. 152

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Berrum-Svennung, 2008[54] RCT Medium	A vs. B Age, median: 74 yrs vs. 71 yrs Age, mean: 71 yrs vs. 69 yrs Sex (male): 69.7% (108/155) vs. 77.6% (118/152) Race: Not reported Smoking status: Not reported Recurrent bladder cancer: 49.7% (77/155) vs. 50.7% (77/152) Stage/Grade: Ta/G1-G2: 85.2% (132/155) vs. 82.2% (125/152); T1/G1-G2: 5.7% (8/155) vs. 8.0%(12/152); Unknown: 9.7% (15/155) vs. 9.9% (15/152) Functional Status: Not reported Size, median (mm): 10 vs. 10 Size, mean (mm): 13 vs. 13 Number of tumors: Single: 56.1% (87/155) vs. 61.2% (93/152); Multiple: 43.9% (68/155) vs. 38.8% (59/152)	A vs. B Recurrence, during 2 years: 51.0% (79/155) vs. 62.5% (95/152); Mann-Whitney U test, p = 0.04, log-rank test, p = 0.022 Progression (stage to muscle invasion): 2.6% (4/155) vs. 1.3% (2/152), (difference "not significant").	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Berrum-Svennung, 2008[54] RCT Medium	NR	NR	NR	NR	Of the 307 patients, 48 (15.6%) were treated with a series of BCG or chemotherapy during the 2-year followup; including 14.8% (23/155) in epirubicin group and 15.8% (24/152) in placebo group, p = 0.80.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Böhle, 2009[55] RCT Medium	Germany and Turkey Number sites: 24 urologic centers Study years (enrollment): January 2004 - June 2005	Papillary, non-muscle-invasive transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Karnofsky performance status ≥ 70%; WBC ≥ 4 X 10^9/L; platelets ≥ 140 X 10^9/L; Hgb ≥ 10g/dL; serum creatine < 2.0 mg/dL; bilirubin < 2.0 mg/dL; AST and ALT < 2.5 times upper limit of normal.	No concomitant CIS or history of CIS; weight loss > 15% during previous 6 months; prior chemotherapy within previous 6 months; more than 3 prior TURs.	A: Gemcitabine (GEM), 2000 mg (in 100 mL saline (0.9% NaCl)), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥ 20 hours. B: Placebo (PBO), 100 mL saline (0.9% NaCl), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥ 20 hours.	Median: 23.6 months (range: 0 - 46). Not reported for each group separately. Cystoscopy at least at month 3 and month 6, and every 6 months thereafter. A second TURBT (no installation) and adjuvant BCG were allowed. If nonmalignancy, CIS, or ≥ pT2 disease detected during TURBT or histopathology, patients were discontinued but followed for safety for 3 months.	Screened: NR Randomized: 355 Postrandomization exclusions (A vs. B): 13 (7.3%) vs. 14 (8.0%) Excluded after treatment (not eligible)(A vs. B): 42 (23.5%) vs. 38 (21.6%) Eligible for efficacy outcomes (A vs. B): 124 (69.3% of randomized) vs. 124 (70.5% of randomized) Lost to followup (A vs. B): 23 (18.5%) vs. 21 (16.9%) Total Analyzed: 248* Per Group Analyzed (A vs. B): 124 vs. 124

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Böhle, 2009[55] RCT Medium	A vs. B Age, median (range): 65 yrs (24 - 89) vs. 67 yrs (39 - 87) Race: NR Sex (male): 76.6% (95/124) vs. 83.1% (103/124) Smoking status: NR Recurrent bladder cancer: 24.2% (30/124) vs. 21.0% (26/124) Stage: pTa: 75.0% (93/124) vs. 71.0% (88/124); pT1: 25.0% (31/124) vs. 29.0% (36/124) Grade: G1: 46.0% (57/124) vs. 53.2% (66/124); G2: 39.5% (49/124) vs. 34.7% (43/124); G3: 10.5% (13/124) vs. 11.3% (14/124); Unknown: 4.0% (5/124) vs. 0.8% (1/124) Multiple lesions: 47.6% vs. 38.7% Functional Status (Karnofski score): score 90-100: 91.9% (114/124) vs. 94.4% (117/124); score 80-85: 7.3% (9/124) vs. 4.0% (5/124); score < 80: 0.8% (1/124) vs. 0.8% (1/124); missing: 0 vs. 0.8% (1/124)	A vs. B Recurrence: 35.5% (44/124) vs. 36.3% (45/124) Progression to muscle-invasive: 2.4% (3/124) vs. 0.8% (1/124) Median recurrence-free survival: 37.2 months vs. 40.2 months; HR (95% CI): 0.946 (0.64-1.39); log-rank test, p = 0.78 12-month recurrence-free rate, % (95% CI): 77.7% (68.8-84.3) vs. 75.3% (66.3-82.3) 24-month recurrence-free rate, % (95% CI): 64.0% (54.1-72.3) vs. 60.7% (51.0-69.1) Mortality, disease-specific: 0.8% (1/124) vs. 0.8% (1/124) Mortality, overall: 2.4% (3/124) vs. 4.8% (6/124)	A vs. B 12-month recurrence-free survival (RFS), %; HR (95% CI): G1/G2: 78.5% vs. 78.4%; 1.05 (0.69-1.59), p = 0.82 G3: 66.7% vs. 42.4%; 0.48 (0.15-1.51), p = 0.21 Single lesion: 84.1% vs. 81.0%; 0.87 (0.49-1.55), p =0.641 Multiple lesions: 71.5% vs. 66.5%; 0.996 (0.57-1.73), p =0.99 Primary tumor: 79.3% vs. 79.8%; 1.05 (0.67-1.63), p = 0.85 Recurrent tumor: 72.2% vs. 58.9%; 0.70 (0.32-1.51), p = 0.36

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Böhle, 2009[55] RCT Medium	A vs. B 12-month recurrence-free survival (RFS), according to receipt of concomitant BCG: With BCG: 61.5% (8/13) vs. 79.4% (17/21): HR = 1.44 (0.49-4.17), p =0.51 Without BCG: 79.9% (89/111) vs. 74.5% (77/103); HR = 0.88 (0.58-1.34), p = 0.55	A vs. B 12-month recurrence-free survival (RFS), according to country: Germany: 77.5% vs. 78.7%: HR = 1.14 (0.73-1.78), p =0.58 Turkey: 78.6% vs. 63.1%; HR = 0.51 (0.23-1.13), p = 0.096	A vs. B All patients receiving installation (GEM = 166; PBO = 162) followed for adverse effects until month 3. At least one adverse event: 29.5% vs. 26.5% Adverse events "possibly related to instillation treatment": 6.6% vs. 3.7% Adverse events reported more than once per group: Alopecia: 1.2% vs. 0% Pyrexia: 1.2% vs. 0.6% Procedural pain: 1.2% vs. 0%	Funded and sponsored by Eli Lilly and Company. The sponsor assisted in the design and conduct of the study; contributed to the management, analysis, interpretation, preparation, and review of the data; and approved the manuscript.	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Cheng, 2005[56] RCT Medium	Hong Kong Single site Study years: July 1986 - November 1991	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Tumor > 1 cm. Multiple or recurrent tumors.	Carcinoma in situ; previous intravesical treatment	A: Doxorubicin, 50 mg (in 50 mL saline), administered intravesically and retained for 2 hours. First installation 2 weeks after TURBT, followed by treatment weekly X 4 weeks, then monthly X 5 months, then 3-monthly X 6 months. B: No adjuvant treatment. TURBT alone. Patients with recurrences in either group were allowed treatment with doxorubicin or other intravesical therapy, such as epirubicin or BCG.	First recurrence, median: 45 months (range: 0 - 190). Progression, median: 128 months (range: 0 to 193) Duration of survival, median: 131.5 months (range: 1 to 193) Not reported for each group separately. Cystoscopy every 3 months for 2 years, then urine cytology every 6 months. Cystoscopy at final examination, if none in previous 1 year.	Screened: 82 Randomized: 82 Postrandomization exclusions: None reported Lost to followup: 1 (not reported which group) Total Analyzed: 82 Per Group Analyzed (A vs. B): 46 vs. 36

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Cheng, 2005[56] RCT Medium	A vs. B Age, mean (SEM): 65.5 yrs (1.7) vs. 62.1 yrs (2.3), p = 0.22 Race: NR Sex (male): 71.7% (33/46) vs. 86.1% (31/36), p = 0.12 Smoking status: NR Recurrent bladder cancer: Not reported Stage: Ta: 67.4% (31/46) vs. 63.9% (23/36); T1: 21.7% (10/46) vs. 13.9% (5/36); Not reported: 10.9% (5/46) vs. 22.2% (8/36); p = 0.52 (Ta and T1) Grade: G1: 34.8% (16/46) vs. 41.7% (15/36); G2: 32.6% (15/46) vs. 19.4% (7/36); G3: 23.9% (11/46) vs. 16.7% (6/36); Not reported: 8.7% (4/46) vs. 22.2% (8/36); p =0.43 (G1/G2/G3) Size (cm): 0.1 - 1.0: 21.7% (10/46) vs. 25.0% (9/36); 1.1 - 3.0: 43.5% (20/46) vs. 27.8% (10/36); 3.1 - 10.0: 23.9% (11/46) vs. 22.2% (8/36); Not reported: 10.9% (5/46) vs. 25.0% (9/36); p = 0.60 (reported categories only) Multiplicity: Single: 50.0% (23/46) vs. 72.2% (26/36); Multiple: 43.5% (20/46) vs. 8.3% (3/36); Not reported: 6.5% (3/46) vs.19.4% (7/36); p = 0.01 (single/multiple categories only) Functional Status: NR	A vs. B Recurrence (one or more): 37.0% (17/46) vs. 52.8% (19/36) Recurrence-free survival (RFS) curve, log rank test, p = 0.12 Median RFS: 190 months vs. 89 months 10-year Kaplan-Meier estimate for RFS: 67% vs. 50% Median time to first recurrence: 13 months (range: 1 - 190) vs. 8 months (range: 1 - 175) Progression (≥ T2; positive lymph node; or distant metastasis): 13.0% (6/46) vs. 5.6% (2/36) Progression-free survival curve, log rank test, p = 0.44 10-year Kaplan-Meier estimate for progression-free survival: 84% vs. 89% Median time to first progression: 34 months vs. 61 months Mortality (disease-specific): 6.5% (3/46) vs. 2.8% (1/36) 10-year Kaplan-Meier estimate for disease-specific survival: 95% vs. 97% Median time to death (disease-specific): 73 months vs. 55 months Mortality (other causes): 30.4% (14/46) vs. 16.7% (6/36) 10-year Kaplan-Meier estimate for overall survival: 68% vs. 83%	In multivariate Cox proportional hazards models: Risk of recurrence increased with larger tumor size (p = 0.013). Risk of progression increased with higher grade (p = 0.004). Tumor stage or number not associated with recurrence or progression.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cheng, 2005[56] RCT Medium	NR	NR	NR	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
De Nunzio, 2011[57] RCT Medium	Italy Single site Study years: January 2000 - December 2009	Cystoscopy-verified primary low-risk bladder tumors. Stage Ta; Grade G1 - G2.	Multiple or large tumors (> 3 cm); Carcinoma in situ; Grade 3 or muscle-invasive on histological exam; History of intravesical therapy within previous year; Upper urinary tract tumor; age ≥ 80 years	A: Mitomycin C (MMC), 40 mg (in 50 mL saline) intravesical; infusion as soon as possible within 24 hours of TURBT; MMC retained in bladder for 1 hour, patient position changed every 15 minutes during instillation; bladder then irrigated for 12 hr with saline solution. B: No adjuvant therapy. After TURBT, irrigation with saline solution until clear.	A vs. B Median (IQR): 90 months (72-109) vs. 85 months (61-112), p = 0.42 Cystoscopy and urine cytology: every 3 months for year 1 and year 2, then every 4 months for year 3 and year 4, then every 6 months for year 5, then every year thereafter.	Screened: NR Randomized: 210 Postrandomization exclusions: none reported Lost to followup: NR Total Analyzed: 102 Per Group Analyzed (A vs. B): 97 vs. 105

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
De Nunzio, 2011[57] RCT Medium	A vs. B Age, median (IQR): 60.8 yrs (52.5-69.2) vs. 61.5 yrs (53.4-69.5), p = 0.34 Race: NR Sex (male): 62.9% (61/97) vs. 68.6% (72/105), p = 0.39 Smoking status: NR Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 70.1% (68/97) vs. 77.1% (81/105), p = 0.26; G2: 29.9% (29/97) vs. 22.9% (24/105), p = 0.25 Size, median (IQR): 1.6 cm (0.6-2.1) vs. 1.8 (0.7-2.2), p = 0.09 Functional Status: NR	A vs. B Overall Recurrence: 10.3% (10/97) vs. 43.8% (46/105), p = 0.001; HR (95% CI): 0.20 (0.10-0.395), p = 0.0001 Early recurrence (within 1 year of enrollment): 40.0% (4/10) vs. 34.8% (16/46), p = 0.008 Early recurrence tumor size, median (IQR): 0.8 cm (0.5-1.0) vs. 0.8 (0.6-1.2), p = 0.34 Early recurrence grade: G1: 75% (3/4) vs. 87.5% (14/16), p = 0.53; G2: 25% (1/4) vs. 12.5% (2/16), p = 0.53; G3: 0% vs. 0%, p = 0.53 Late recurrence (after 1 year of enrollment): 60.0% (6/10) vs. 60.9% (28/46), p = 0.0001 Late recurrence tumor size, median (IQR): 1.2 cm (1.0-1.5) vs. 1.5 (1.0-1.7), p = 0.001 Late recurrence grade: G1: 66.7% (4/6) vs. 71.4% (20/28), p = 0.60; G2: 33.3% (2/6) vs. 21.4% (6/28), p = 0.60; G3: 0% vs. 0% (0/6) vs. 7.1% (2/28), p = 0.60 Progression (≥ T2): 0% (0/97) vs. 0.95% (1/105), p = 0.33 All recurrences in treatment arm were Ta; 30.4% (14/46) of recurrences in control arm were T1. Absolute risk reduction (MMC vs control): Overall = 31%, Early recurrence = 11%, Late recurrence = 20% NNT to prevent one recurrence: Overall = 3.26, Early recurrence = 8.99; Late recurrence = 5.12	NR

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Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
De Nunzio, 2011[57] RCT Medium	NR	NR	NR	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Ersoy, 2013[58] RCT High	Turkey Single site Study years: February 2006 - November 2010	Primary low-risk non-muscle-invasive bladder cancer (NMIBC). Stage Ta, Grade G1. Solitary tumor; Size < 3 cm.	"Medium or high risk NMIBC"; Muscle-invasive bladder cancer; Suspected bladder perforation.	A: Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.	A vs. B vs, C Median (range): 51 months (12-60) vs. 50 months (12-59) vs. 54 months (38-60), p = 0.815 Cystoscopy: month 3, month 12, then annually for 5 years. Patients with macroscopic or microscopic hematuria underwent ultrasound and cystoscopy. Urinary pH (groups A and B only): measured night before TURBT and just prior to TURBT.	Screened: NR Randomized: 53 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 49 Per Group Analyzed (A vs. B vs. C): 11 vs. 15 vs. 23

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ersoy, 2013[58] RCT High	A vs. B vs. C Age, mean (± SD): 59.3 yrs (± 14.9) vs. 63.5 yrs (± 15.0) vs. 61.9 yrs (± 10.2), p = 0.716 Race: NR Sex (male): 81.8% (9/11) vs. 86.7% (13/15) vs. 95.7% (22/23), p = 0.395 "History of smoking": "None": 36.4% vs. 26.7% vs. 8.7%; "Present": 63.6% vs. 73.3% vs. 91.3%; p = 0.124 (for "History of Smoking") Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 100% vs. 100% Functional Status: NR	A vs. B vs. C Recurrence free at 1 year: 100% vs. 86.7% vs. 91.3%; A vs. B, p = 0.132; A vs. C, p = 0.173 Recurrence free at 3 years: 100% vs. 79.4% vs. 82.6%; A vs. B, p = 0.132; B vs. C, p = 0.645 Recurrence free at 5 years: 100% vs. 79.4% vs. 82.6%; A vs. C, p = 0.173; B vs. C, p = 0.645 Mean time to recurrence, months (95% CI): NA vs. 34.8 (28.5-41.1) vs. 51.8 (47.7-57.7)	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ersoy, 2013[58] RCT High	NR	A vs. B vs. C Recurrence free survival according to sex, (p = 0.769): Male, 1-year: 90.9%; 3-years: 85.9%; 5-years: 85.9% Female, 1-year: 100.0%; 3-years: 66.7%; 5-years: NR Mean time to recurrence according to sex, months (95% CI): Male: 53.0 (47.7-58.2) Female: 44.9 (28.6-61.1) Recurrence free survival according to history of smoking (p =0.645): None, 1-year: 100.0%; 3-year: 85.7%; 5-years: 85.7% Present, 1-year: 89.7%; 3-years: 84.2%; 5-years: 84.2% Mean time to recurrence according to history of smoking, months (95% CI): None: 54.9 (45.8-64.1) Present: 52.1 (46.3-57.9)	NR	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Giannakopoulos, S, 1998[2] RCT Medium	Greece Number sites: Unclear (authors from 3 centers) Study years: NR	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Stage ≥ T2. Grade G1 or G3 (any stage). CIS; Other concomitant malignancy; Serious systemic disease; Previous intravesical chemotherapy or immunotherapy; TCC of upper urinary tract; Previous systemic chemo/immunotherapy or pelvic radiation therapy	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (IFN-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (IFN-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (IFN-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First installation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Installations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	36 months; Not reported as median/mean, nor for each group. Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter. Biopsy of previous scars and random bladder biopsies every 3 months for 18 months, and every 6 months thereafter. CBC and serum chemistry tests at every other installation.	Screened: NR Randomized: 89 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 89 Per Group Analyzed (A vs. B vs. C vs. D): 20 vs. 22 vs. 24 vs. 23

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Giannakopoulos, S, 1998[2] RCT Medium	A vs. B vs. C vs. D Age, mean (SD): 61.6 yrs (9.62) vs. 62.1 yrs (9.49) vs. 60.9 yrs (9.43) vs. 61.9 yrs (9.98); p > 0.10 Race: NR Sex (male): 80.0% (16/20) vs. 81.8% (18/22) vs. 79.2% (19/24) vs. 82.6% (19/23); p > 0.10 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 60.0% (12/20) vs. 59.1% (13/22) vs. 62.5% (15/24) vs. 56.5% (13/23); T1: 40.0% (8/20) vs. 40.9% (9/22) vs. 37.5% (9/24) vs. 43.5% (10/23); p > 0.10 Grade: All G2 Functional Status: NR	A vs. B vs. C vs. D Recurrence: 65.0% (13/20) vs. 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); A vs. B, p = 0.06; A vs. C, p < 0.05; A vs. D, p < 0.01; Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): 15.0 vs. 21.4 vs. 26.1 vs. 30.0; A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: 2.91 vs. 1.19 vs. 0.88 vs. 0.63; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: 30.0% (6/20) vs. 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); A vs. B, p = NS; A vs. C, p < 0.05; A vs. D, p < 0.05; B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS. Progression details: A: Ta to T1 (n = 3), T1 to MIBC (n = 3); B: Ta to T1 (n = 1), T1 to MIBC (n = 2); C: T1 to MIBC (n = 1); D: T1 to MIBC (n = 1).	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 53.8% (7/13) vs. 50.0% (4/8) vs. 57.1% (4/7) vs. 40.0% (2/5); For all comparisons between groups, p > 0.10. T1: 46.2% (6/13) vs. 50.0% (4/8) vs. 42.9% (3/7) vs. 60.0% (3/5); For all comparisons between groups, p > 0.10. Recurrence-free survival time according to stage, Mean months (SD): Ta: 15.4 (5.86) vs. 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); A vs. B, p < 0.01; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.05, B vs. D, p < 0.001; C vs. D, p = NS. T1: 14.5 (6.95) vs. 19.5 (9.33) vs. 23.0 (9.17) vs. 29.0 (7.55); A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.048, B vs. D, p < 0.001; C vs. D, p < 0.01. Recurrence rate per 100 patient-months according to stage: Ta: 2.43 vs. 0.96 vs. 0.78 vs. 0.44; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p<0.001; Differences between B, C, and D, p = NS. T1: 3.77 vs. 1.55 vs. 1.05 vs. 0.8; Results "similar" to stage Ta, no p=values reported

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Giannakopoulos, S, 1998[2] RCT Medium	B vs. C vs. D Simple recurrence rate: Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS.	NR	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups not reported) developed fevers and were found to have urinary tract infections.	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Gudjónsson, 2009[59] RCT Medium	Sweden Number sites: Multi-center. Number unclear (authors from 8 centers) Study years: 1997 - 2004	Low to intermediate risk bladder tumors (primary or recurrent). Stages Ta or T1; Grade G1 or G2. Single or multiple tumors. No upper limit on size.	CIS; Grade 3 cancer; Muscle-invasive tumor. History of high-risk tumor (G3 or CIS) and intravesical therapy within previous year; upper urinary tract tumor; age > 85 years. Patients with muscle invasion on re-TURBT. Histopathology report could not confirm malignancy.	A: Epirubicin, 80 mg (in 30 mL saline) intravesically as soon as possible within 24 hours of TURBT. A single installation, retained intravesically for 1 hour; fluid restriction and patient position changed every 15 minutes. B: No adjuvant treatment. TURBT alone.	Median followup (all patients): 3.9 years. Not reported for each group. Median followup (patients without recurrence): 3.6 years (range: 0.4 - 7.4 years) Cystoscopy and urine cytology, every 3 months during year 1, and every 4 months during year 2. Thereafter, surveillance performed according to local routines at each center.	Screened: NR Randomized: 305 Postrandomization exclusions: 9 Lost to followup: 6 Total Analyzed: 219 Per Group Analyzed: 102 vs. 117

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gudjónsson, 2009[59] RCT Medium	A vs. B Age, median (yrs)/mean (yrs): 71/70 vs.72/70 Race: NR Sex (male): 72.5% (74/102) vs. 69.3% (81/117) Smoking status: NR Recurrent bladder cancer: 46.1% (47/102) vs. 48.7% (57/117) Stage: Ta: 81.4% (83/102) vs. 86.3% (101/117) ; T1: 9.8% (10/102) vs. 6.8% (8/117) ; Unknown: 7.8% (8/102) vs. 6.0% (7/117) ; "Low malignant potential": 1.0% (1/102) vs. 0.9% (1/117) Grade: G1: 53.9% (55/102) vs. 48.7% (57/117) ; G2: 39.2% (40/102) vs. 44.4% (52/117) ; Unknown: 6.9% (7/102) vs. 6.8% (8/117) Functional Status: NR Number of tumors: 1: 44% (45/102) vs. 46% (54/117); 2-3: 21% (21/102) vs. 27% (32/117); ≥ 4: 33% (34/102) vs. 26% (30/117) All comparisons between the two groups statistically non-significant (p-values between 1.0 and 0.34)	A vs. B Recurrence: 62% (63/102) vs. 77% (90/117) Difference in Recurrence-free survival, p = 0.016 Univariate HR (95% CI): 0.67 (0.49-0.93), p = 0.017 Multivariate HR (95% CI), adjusting for tumor multiplicity, number of recurrences/year, sex, age, and tumor grade: 0.56 (0.39-0.80), p = 0.002	A vs. B Recurrence rate according to primary or recurrent tumor: Primary: 40% (22/55) vs. 67% (40/60), p = 0.008 Recurrent: 87% (41/47) vs. 88% (50/57), p = 0.49 Recurrence rate according to solitary or multiple tumors: Solitary: 36% (16/45) vs. 67% (36/54), p = 0.004 Multiple: 84% (46/55) vs. 85% (53/62), p = 0.26

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gudjónsson, 2009[59] RCT Medium	NR	NR	NR	FoU Kronoberg; Swedish Cancer Society; Skane County Council Research and Development Foundation	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Gustafson, 1991[60] RCT Medium	Sweden Number sites: Unclear. Authors from 4 centers Study years: NR	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	None explicitly stated. However, no patient had previously been treated with radiotherapy, systemic or topical chemotherapy.	A: Mitomycin C. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 ml" to "40 mg in 250 ml". First installation approximately 2 weeks after TURBT. Installations weekly X 4 weeks, then monthly X 11 months. B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 ml" to "80 mg in 250 ml". First installation approximately 2 weeks after TURBT. Installations weekly X 4 weeks, then monthly X 11 months. C: No adjuvant treatment. TURBT alone.	A vs. B vs. C Mean followup, months (range): 47 (12-65) vs. 45 (14-69) vs. 35 (10-68) Cystoscopy every 3 months during year 1; thereafter, every 6 months unless recurrence, in which case every 3 months. Micturition frequency, pain on micturition, other subjective symptoms recorded before and after each installation. Blood tests (including CBC and creatinine) after 2nd and 4th installation and every month, thereafter.	Screened: NR Randomized: 62 Postrandomization exclusions: NR Lost to followup: 2 Total Analyzed: 60 Per Group Analyzed: 19 vs. 20 vs. 21

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gustafson, 1991[60] RCT Medium	A vs. B vs. C Age, mean (Overall; not reported by group): 67 years Race: NR Sex (Overall male: female; not reported by group): "Four to one" Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 89.5% (17/19) vs. 90.0% (18/20) vs. 95.2% (20/21); T1: 10.5% (2/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Grade: G1: 36.8% (7/19) vs. 35.0% (7/20) vs. 33.3% (7/21); G2: 63.2% (12/19) vs. 65.0% (13/20) vs. 61.9% (13/21); G3: 0% (0/19) vs. 0% (0/20) vs. 4.8% (1/21) Functional Status: NR	A vs. B vs. C Recurrence: Tumor-free survival during treatment year: 52.6% (10/19) vs. 15% (3/20) vs. 14.3% (3/21) Tumor-free survival for duration of followup: 26.3% (5/19) vs. 10% (2/20) vs. 4.8% (1/21) Mean disease-free interval, months (A vs. B): 14 vs. 6, p = 0.02 Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p = 0.02 Progression: Increased stage: 0% (0/19) vs. 5% (1/20) vs. 4.8% (1/21) Increased grade: 0% (0/19) vs. 15% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10% (2/20) vs. 0% (0/21)	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gustafson, 1991[60] RCT Medium	NR	NR	No significant changes in frequency of micturition. No serious side-effects detected by blood samples. Mild pain on micturition (A vs. B): 60 % vs. 45%	King Gustaf V Jubilee Foundation	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Herr, 1988[61] RCT Medium Herr, 1995[62] (10 year followup) Cookson, 1997[63] (15 year followup) Herr, 1997[64] (15 year followup Subgroup analysis) Pinsky, 1985[65]	USA 1978-1981	Recurrent, superficial transitional-cell carcinoma of the bladder (Ta, T1, Tis) <u>Subgroup analysis:</u> T1 tumors Grade 2-3		3-5 weeks after TURBT began weekly treatments for 6 weeks: A. TURBT B. TURBT plus BCG 120 mg (Armand Frappier strain) in 50 ml saline	Cytology and cystoscopy every 3-6 months Median followup 72 months (14-108 months) <u>10 year followup:</u> Median followup: 108 vs 140 months <u>15 year followup:</u> median 184 months <u>15 year Subgroup analysis:</u> 15 years	Screened: Not reported Randomized: 88 Post-randomization exclusions: 2 (withdrew after randomization) Loss to followup: Last followup are tick marks on graph Analyzed: 86 (43 vs 43) <u>10 year followup:</u> Analyzed: 43 vs 43 <u>15 year followup:</u> Loss to followup: 2 TURBT patients Analyzed: 84 (41 vs 43) <u>15 yr Subgroup analysis:</u> Randomized: 48 (39 patients received one or more courses of BCG Analyzed: 48 (23 vs 25)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Herr, 1988[61] RCT Medium Herr, 1995[62] (10 year followup) Cookson, 1997[63] (15 year followup) Herr, 1997[64] (15 year followup Subgroup analysis) Pinsky, 1985[65]	Age (median) 60 vs 61 Male: 77% vs 74% Race: Not reported Smoking: Not reported Stage: Ta: 31 (72%) vs 30 (70%) T1: 12 (28%) vs (30%) +TIS: 26 (60%) vs 23 (53%) <u>15 yr Subgroup analysis:</u> Age (median): 59 Male: 32/48 (67%) Stage:T1: 5 (10%) T1 + Tis: 43 (90%)	Progression based on T stage: 41 (95%) vs 23 (53%) Median progression-free interval: 12 months vs 60 months Died due to bladder cancer: 14 vs 6 <u>10 year followup:</u> Progression based on invasion of bladder muscle or metastases: 26 (60%) vs 16 (37%) Died of bladder cancer: 17 vs 10 <u>15 year followup:</u> Progression based on muscle invasion, node positive disease, metastases: 23 (53%) vs 23 (53%) <u>15 yr Subgroup analysis:</u> Progression-free survival: 15 (65%) vs 10 (40%)	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Herr, 1988[61] RCT Medium Herr, 1995[62] (10 year followup) Cookson, 1997[63] (15 year followup) Herr, 1997[64] (15 year followup Subgroup analysis) Pinsky, 1985[65]			Not reported	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Hirao, 1992[66] RCT Medium	Japan Number sites: Single center (multiple hospitals) Study years: November 1, 1986 - March 30, 1990	Superficial bladder cancer. Primary only. Stages ≤ pT1b; Grade ≤ G2. Single or multiple tumors.	Muscle invasion or grade G3 detected by postoperative pathological exam.	A:Thio-TEPA, 30 mg (in 30 ml physiological saline), for a total of 32 installations over a 2-year period. Initial treatment was maintained until 3rd recurrence or disease progression. B: No adjuvant therapy. TURBT only.	A vs. B Mean followup, months (range): 19.6 ± 10.8 (1-38) vs. 14.9 ± 10.7 (1-42) Cystoscopy and urinary cytology every 3 months for 3 years, every 6 months thereafter "until at least 5 years".	Screened: NR Randomized: 103 (2 groups: 52 vs. 51) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 93 (2 groups) Per Group Analyzed: 45 vs. 48

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Hirao, 1992[66] RCT Medium	A vs. B Age, mean (years): 59.1 (± 12.9) vs. 64.2 (± 12.2) Race: NR Sex (male): 73.1% (38/45) vs. 76.5% (39/48) Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 31.1% (14/45) vs. 41.7% (20/48); T1: 68.9% (31/45) vs. 58.3% (28/48) Grade: G1: 8.9% (4/45) vs. 22.9% (11/48); G2: 91.1% (41/45) vs. 77.1% (37/48) Multiplicity: Solitary: 35.6% (16/45) vs. 31.3% (15/48); Multiple: 64.4% (29/45) vs. 68.8% (33/48) Functional Status: NR No significant differences in any characteristic, except lower mean age of group A.	A vs. B Recurrence at 3 years: 15% vs. 46%, $p < 0.05$ Cumulative recurrence rate (CRR)*, all cases: 0.70 vs. 3.07 * CRR is 100 X total # recurrences/total followup period in months.	Non-recurrence rates at 3 years, according to stage: G1, no significant difference between groups; G2, A > B significant. Non-recurrence rates at 3 years, according to grade: Ta, no significant difference between groups; T1, A > B significant. Non-recurrence rates at 3 years, according to tumor multiplicity: single tumor, no significant difference between groups; Multiple tumors, A > B significant. Cumulative recurrence rate (CRR): Ta: 0.97 vs. 2.03 T1: 0.55 vs. 3.80 G1: 1.33 vs. 1.92 G2: 0.64 vs. 3.99 Solitary: 0.77 vs. 2.44 Multiple: 0.48 vs. 4.86

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hirao, 1992[66] RCT Medium	NR	NR	Group A: Irritable bladder: n = 1 (8.9%) Contracted bladder: n = 1 (2.2%) Leukopenia: n = 1 (2.2%) Dermatitis: n = 1 (2.2%) Group B: NR	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Igawa, 1996[67] RCT Medium	Japan Number sites: Unclear. Authors from 3 centers Study years: NR	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	None reported	A: Epirubicin, 20 mg (in 40 mL saline). First installation within 2 weeks of TURBT, retained in bladder X 2 hours; Once a month X 24 months (Total 24 installations). B: No adjuvant treatment. TURBT alone.	Median followup, overall: 20 months (range 3-42). Cystoscopy every 3 months X 2 years, then every 6 months thereafter.	Screened: NR Randomized: 82 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 75 Per Group Analyzed: 43 vs. 32

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Igawa, 1996[67] RCT Medium	Population characteristics not reported according to treatment status (see comment).	A vs. B Recurrence: 60.5% (26/43) vs. 68.8% (22/32), p-value not reported. Progression: 20.9% (9/43) vs. 3.1% (1/32), p = 0.024	A vs. B [reported for Biopsy (+) (concomitant dysplasia/CIS) and Biopsy (-) status] Recurrence: Biopsy (+): 100% (10/10) vs. 75.0% (6/8), p = 0.36; Biopsy (-): 48.5% (16/33) vs. 66.7% (16/24), p = 0.27. Recurrence-free survival: Biopsy (+): B > A, log-rank test = NS, p-value not reported; Biopsy (-): A > B, log-rank test = NS, p-value not reported. Mean time (months) to recurrence: Biopsy (+):9.0 vs. 10.9, p = 0.72; Biopsy (-): 9.6 vs. 7.3, p = 0.37. Progression (stage): Biopsy (+): 10.0% (1/10) vs. 0.0% (0/8), p > 0.95; Biopsy (-): 3.0% (1/33) vs. 0.0% (0/24), p > 0.95. Progression (grade): Biopsy (+): 40.0% (4/10) vs. 0.0% (0/8), p = 0.23; Biopsy (-): 9.1% (3/33) vs. 4.2% (1/24), p > 0.09.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Igawa, 1996[67] RCT Medium	NR	NR	NR	NR	Principal focus of the study was comparison of patients with and without concomitant urothelial dysplasia or CIS, as determined by biopsy of apparently normal urothelium after TURBT. These two groups (biopsy + / biopsy -) were each randomized to receive epirubicin or not. Baseline patient characteristics were only reported according to dysplasia/CIS status.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Koga, 2010[68] RCT Medium	Japan Multicenter 2002-2005	Histologically-confirmed Ta, T1 transitional cell carcinoma or CIS of bladder	History of BCG intravesical instillation therapy, severe bladder irritation before start of drug administration, infravesical instillation therapy with an anticancer drug within 3 weeks before start of BCG	BCG 80 mg (Tokyo strain) within 4 weeks of biopsy or TURBT and repeated weekly for 8 weeks; patients with complete response were randomized to: A. BCG 80 mg (Tokyo strain) within 3 months of randomization followed by instillations at 3, 6, and 9 months B. No BCG	Cytology and cystoscopy 2 months after randomization and then every 3 months for 3 years and thereafter every 6 months Median followup: 27 vs 29 months	Number screened: 63 Randomized: 53 (26 vs 27) Post-randomization exclusions: 2 in BCG group withdrew before start of maintenance instillations Loss to followup: None reported Analyzed: 51 (24 vs 27)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Koga, 2010[68] RCT Medium	Age <70: 9 vs 14 Age ≥70 : 15 vs 13 Male: 79% vs 78% Race: Not reported Smoking: 15 (63% vs 20 (74%) Stage: Ta/T1: 3 (13%) vs 2 (7%) CIS: 21 (88%) vs 25 (93%)	Recurrence: 1 (4%) vs 7 (26%), p=0.078 Progression: 0 vs 1 (4%) Mortality: 2 (8%) vs 2 (7%) Died due to bladder cancer: 0 vs 1 (4%)	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Koga, 2010[68] RCT Medium			Dysuria: 17% vs NR	Japan BCG Laboratory Co. Ltd.	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Koontz, 1981[69] (prophylaxis) RCT Medium	USA Multicenter 1974-1977	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 ml distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 ml distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa	Cystoscopy every 3 months followup: Mean not reported, 16 patients followed for <2 years (median 15 months)	Screened: Not reported Randomized: 95 Postrandomization exclusions: 2 Loss to followup: Not reported Analyzed: 93 (23 vs. 23. vs. 47)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Koontz, 1981[69] (prophylaxis) RCT Medium	Age (median): 65 years Male: 88% Race: Not reported Smoking status: Not reported Primary: Unclear Stage: Not reported Grade: Not reported Multifocal: Unclear Tumor size: Not reported	% recurrence-free at 12 months: 63% vs. 69% vs. 40% (p=0.02 for A or B vs. C)	A or B vs. C % recurrence-free at 12 months Cytology positive: 56% vs. 40% Cytology negative: 69% vs. 40%

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Koontz, 1981[69] (prophylaxis) RCT Medium			Leukopenia (WBC <3000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) Thrombocytopenia (platelets <100,000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) UTI: 0% (0/23) vs. 17% (4/23) vs. 0% (0/47)	Not reported	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Krege, 1996[70] RCT Medium	Germany, Multicenter 1985-1992	histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3), no intravesical chemotherapy during last 6 months or previous radiation	Primary stage pTa grade 1 tumor	A. TURBT only B. TURBT + MMC 20 mg in 50 ml saline every 2 weeks during year 1 and monthly during year 2 C. TURBT + BCG 120 mg (Connaught strain) in 50 ml saline and subcutaneous BCG 0.5 mg in the forearm weekly for 6 weeks and then monthly for 4 months	Evaluated after 3, 6, 9, 12, 18, 24, 30, and 36 months Mean followup: 20 months	Number screened: Not reported Randomized: 337 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 336 (122 vs 112 vs 102)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Krege, 1996[70] RCT Medium	Age (mean): 65 (not specified by group) Male: 75% vs 84% vs 80% Race: Not reported Smoking: Not reported Stage: Ta: 95 (78%) vs 84 (74%) vs 78 (77%) T1: 27 (22%) vs 29 (26%) vs 24 (24%) Grade: Grade 1: 47 (39%) vs 40 (39%) vs 36 (41%) Grade 2: 69 (57%) vs 57 (51%) vs 57 (56%) Grade 3: 6 (5%) vs 12 (11%) vs 4 (4%)	Recurrence: 56 46%) vs 30 (25%) vs 26 (25%)	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Krege, 1996[70] RCT Medium			Cystitis: NR vs 16% vs 34% Hematuria: NR vs 3% vs 6% Fever: NR vs 0 vs 18	Ministry of Science and Technology, Germany	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Kurth, 1997[71] RCT (followup of Kurth, 1984[72]) Medium	Europe (multinational) Number sites: 21 Study years: December 1979 - December 1983	Histologically proved, transurethrally resectable transitional cell carcinoma of the bladder or carcinoma in situ (primary or recurrent). Stages Ta or T1; Grade G0, G1, G2 or G3.	None reported	A: Doxorubicin, 50 mg (in 50 ml normal saline). First installation 3 to 14 days after TURBT and retained for 1 hour. Then, weekly for 1 month, then monthly for 11 months. Nitrofurantoin, 100 mg, was given after each instillation 3 times/day X 3 days. WBC, platelets, and urinalysis before each installation. Chemotherapy delayed until WBC ≥ 4 X 109/L and platelets ≥ 1.5 X 109/L; or until any bacterial cystitis was controlled. B: No adjuvant treatment. TURBT alone.	Median followup (Overall; not reported by groups): For recurrence: 3.4 years For Invasion: 5 years For Time to death from malignancy: 7.2 years For Survival: 10.7 (maximum followup 14 years). Cystoscopy every 12 weeks during year 1, every 16 weeks during year 2, and every 24 weeks thereafter. If cytology was positive and no lesion was visible on cystoscopy, random biopsies were done. "Patients themselves performed the documentation". Patients "received from a central coordinator a form with data on the instillations and cytoscopic controls".	A vs. B Screened: NR Randomized: 264 (2 groups: 191 vs. 73) Postrandomization exclusions: NR Analyzed for Recurrence: 236 (166 vs. 70) Total Analyzed for Progression and Survival: 252 (181 vs. 72)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Kurth, 1997[71] RCT (followup of Kurth, 1984[72]) Medium	A vs. B Age: < 50 years: 8% vs. 7% 50-59 years: 21% vs. 28% 60-69 years: 28% vs. 35% 70-79 years: 39% vs. 24% ≥ 80: 4% vs. 7% Unknown: 1% vs. 0% Race: NR Sex (male): 80% (145/182) vs. 90% (65/72); Unknown: 1% (1/182) vs. 0% (0/72) Smoking status: NR Recurrent bladder cancer: 30.2% (55/182) vs. 34.7% (25/72); Unknown: 1% (1/182) vs. 0% (0/72) Stage: T0: 0% (0/182) vs. 0% (0/72); Ta: 50% (91/182) vs. 58% (42/72); T1: 45% (82/182) vs. 40% (29/72); Tis: 4% (7/182) vs. 1% (1/72); Unknown: 1% (1/182) vs. 0% (0/72) Grade: G0: 8% (15/182) vs. 15% (11/72); G1: 43% (78/182) vs. 40% (29/72); G2: 33% (59/182) vs. 36% (26/72); G3: 12% (22/182) vs. 1% (1/72); Unknown: 4% (7/182) vs. 5% (4/72) Functional Status: NR	A vs. B Recurrence: 50% (83/166) vs. 67% (47/70) Recurrence rate per year: 0.30 vs. 0.68; p-value significant. Recurrence-free at 3 years: 48% (95% CI: 40-56) vs. 29% (95% CI: 17-41) Time to first recurrence: A > B, p < 0.001. Progression to ≥ stage T2: 13.8% (25/181) vs. 18.1% (13/72) Progression-free (≥ stage T2) at 5 years: 86% (95% CI: 80-92) vs. 87% (95% CI: 77-96) Free of distant metastases at 5 years: 97% (95% CI: 94-100) vs. 98% (95% CI: 95-100) Survival (all cause) at 5 years: 74% (95% CI: 67-81) vs. 73% (95% CI: 61-84) Survival (all cause) at 10 years: 46% (95% CI: 37-54) vs. 42% (95% CI: 29-56) Survival (death from malignancy) at 5 years: 92% (95% CI: 88-96) vs. 97% (95% CI: 92-100) Survival (death from malignancy) at 10 years: 82% (95% CI: 75-89) vs. 82% (95% CI: 70-95)	A (n = 86) vs. B (n = 69) [preliminary results reported for a subset of patients; average followup approximately 1 year]* Recurrence rate/100 patient-months: Primary tumor (n = 48 vs. n = 43): 3.10 vs. 4.81, p = NS Recurrent tumor (n = 38 vs. n = 26): 5.41 vs. 11.45, p = 0.026 * from Kurth, 1984

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kurth, 1997[71] RCT (followup of Kurth, 1984[72]) Medium	NR	NR	Group A only (data for n = 176); not reported for group B Bacterial cystitis: 14.2% (25/176) Chemical cystitis: 2.8% (5/176) Systemic side effects: 5.1% (9/176) [allergic reaction, mild nausea, diarrhea, and vomiting]	National Cancer Institute	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Lamm, 2000[73] RCT Medium Lerner, 2007[74] SWOG 8507	USA Multicenter 1986-1989	Histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment; papillary tumors Ta or T1; 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or CIS	Stage T2 or higher, previous radiation therapy for bladder, planning concomitant chemotherapy or radiation therapy, received previous BCG treatments	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 ml saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks then randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years B. No BCG	Cytology and cystoscopy every 3 months for 2 years then every 6 months for 2 years then yearly Median followup: 120 months	Number screened: 660 Randomized: 550 Post-randomization exclusions: 12 deemed ineligible before randomization; 154 had evidence of disease at randomization and were not included Analyzed: 384 (192 vs 192)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Lamm, 2000[73] RCT Medium Lerner, 2007[74] SWOG 8507	Age (mean): 67 vs 67 Male: 90% vs 83% Black men: 4% vs 3% Smoking: Not reported CIS at induction: 66 (34%) vs 64 (33%)	5 year survival: 83% vs 78%	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lamm, 2000[73] RCT Medium Lerner, 2007[74] SWOG 8507			2 BCG related deaths	National Cancer Institute	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Matsumura, 1992[75] RCT Medium	Japan Number sites: Unclear (multicenter) July 1987 - December 1989	Transitional-cell carcinoma of the bladder. Primary (only with multiple lesions) or recurrent. Stages Tis, Ta, or T1; Grade G0, G1, G2 or G3.	None reported	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 installations over 2 years, after TURBT: Timing of first dose not specified; installations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4. B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 installations over 2 weeks before TURBT; specific schedule not reported. C: No adjuvant treatment. TURBT alone.	240 days, overall. (n = 284) 720 days (maximum), overall, not reported by group. (n = 156) followup methods not reported.	Screened: NR Randomized: 443 (182 vs. 126 vs. 135) Postrandomization exclusions: 42 (16 vs. 13 vs. 13) Lost to followup: 26 (not reported by group) Total Analyzed: 284 (126 vs. 75 vs. 83)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Matsumura, 1992[75] RCT Medium	A vs. B vs. C Age: ≤ 49 years: 7.1% (9/126) vs. 4.0% (3/75) vs. 12.1% (10/83); 50-59 years: 15.1% (19/126) vs. 20.0% (15/75) vs. 13.3% (11/83); 60-69 years: 34.1% (43/126) vs. 32.0% (24/75) vs. 31.3% (26/83); ≥ 70 years: 42.9% (54/126) vs. 44.0% (33/75) vs. 42.2% (35/83); age overall, p = NS Race: NR Sex (male): 81.7% (103/126) vs. 78.7% (59/75) vs. 84.3% (70/83), p = NS Smoking status: NR Recurrent bladder cancer: 59.5% (75/126) vs. 61.3% (46/75) vs. 50.6% (42/83), p = NS Stage: Ta: 32.5% (41/126) vs. 20.6% (26/75) vs. 32.5% (27/83); T1: 42.9% (54/126) vs. 20.6% (26/75) vs. 36.1% (30/83); Tis: 0.8% (1/126) vs. 2.7% (2/75) vs. 3.6% (3/83); Unknown: 23.8% (30/126) vs. 28.0% (21/75) vs. 26.5% (22/83); p = NS Grade: G0: 2.4% (3/126) vs. 8.0% (6/75) vs. 2.4% (2/83); G1: 33.3% (42/126) vs. 34.7% (26/75) vs. 32.5% (27/83); G2: 36.5% (46/126) vs. 30.7% (23/75) vs. 36.1% (30/83); G3: 4.0% (5/126) vs. 4.0% (3/75) vs. 0.0% (0/83); Unknown: 23.8% (30/126) vs. 22.7% (17/75) vs. 28.9% (24/83); p = NS Functional Status: NR Size: ≈ 1 cm: 52.4% (66/126) vs. 49.3% (37/75) vs. 55.4% (46/83); ≈ 3 cm: 34.1% (43/126) vs. 42.7% (32/75) vs. 33.7% (28/83); ≈ 5 cm: 7.1% (9/126) vs. 6.7% (5/75) vs. 7.2% (6/83); > 5 cm: 0.8% (1/126) vs. 1.3% (1/75) vs. 1.2% (1/83); Unknown: 5.6% (7/126) vs. 0.0% (0/75) vs. 2.4% (2/83); p = NS Multiplicity: Single: 26.2% (33/126) vs. 22.7% (17/75) vs. 24.1% (20/83); 2-4: 58.7% (74/126) vs. 46.7% (35/75) vs. 54.2% (45/83); ≥ 5: 11.9% (15/126) vs. 25.3% (19/75) vs. 18.1% (15/83); Unknown: 2.4% (3/126) vs. 2.7% (2/75) vs. 2.4% (2/83); p = NS	A vs. B vs. C Recurrence-free survival rate at 240 days: 73.8% vs. 57.8% vs. 61.2%; A vs. B, p < 0.05; other comparisons, p = NS Recurrence-free survival rate at 480 days: 52.0% vs. 37.0% vs. 32.0%; A vs. C, p < 0.01; other comparisons, p = NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8% vs. 17.8%; A vs. B, p < 0.05; A vs. C, p < 0.01; other comparisons, p = NS	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsumura, 1992[75] RCT Medium	A vs. B Recurrence-free survival rate at 240 days: 73.8% vs. 57.8%, p < 0.05 Recurrence-free survival rate at 480 days: 52.0% vs. 37.0%, p = NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8%, p < 0.05	NR	A vs. B (not reported for group C) Pollakiuria: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75) Contracted bladder: 0.0% (0/126) vs. 1.3% (1/75)	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Melekos, 1990[76] RCT Medium	Greece Number of centers not reported Study years not reported	Superficial bladder carcinoma (Ta and T1)		A. TURBT B. TURBT plus BCG 150 mg (Pasteur F) in 50 ml saline 2-3 weeks after last TURBT and then weekly for 8 weeks and then maintenance BCG every 3-5 days after each followup evaluation when	Cytology and cystoscopy every 3 months for 24 months Mean followup: 30 vs 29 months	Screened: Not reported Randomized: 100 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 100 (33 vs 67)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Melekos, 1990[76] RCT Medium	Age (mean): 68 vs 68 Male: 85% vs 85% Race: Not reported Smoking: Not reported Stage: Ta: 16 (48%) vs 27 (40%) T1: 17 (52%) vs 40 (60%) Grade: Grade 1: 11 (33%) vs 24 (36%) Grade 2: 19 (58%) vs 34 (51%) Grade 3: 3 (9%) vs 9 (13%)	Patients with recurrences: 19 (58%) vs 22 (33%), p<0.05 Mean interval to tumor recurrences, months: 10 vs 13, p<0.05 Tumor progression in stage: 8 (24%) vs 4 (6%), p<0.01 Tumor progression in grade: 5 (15%0 vs 3 (4%), p<0.01	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1990[76] RCT Medium			Irritative vesical symptoms: 84% Fever: 27% Macroscopic hematuria: 21% Influenza-like syndrome: 10%	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Melekos, 1992[77] RCT Medium	Greece Number sites: Unclear (authors from two centers) Study years: NR	Histologically proved superficial carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3.	CIS; Existence of another cancer; History of another cancer outside the bladder; Previous local or systemic chemotherapy or radiotherapy.	A: Epirubicin, 50 mg (in 5 mL sterile saline), retained in bladder for 1.5 hours. First installation within 2 weeks after TURBT; One dose weekly X 6 weeks (Total 6 installations for all patients). Then, single dose given at each followup exam for patients who were recurrence-free during following 2 years (maximum 7 additional installations). Antimicrobial agents given orally for 2-3 days after each installation. B: No adjuvant treatment. TURBT alone.	Duration of followup not reported. Cystoscopy and urinary cytology every 3 months X 1 year, then every 4 months X 1 year, then every 6 months thereafter.	Screened: NR Randomized: 80 (2:1, but numbers not reported) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 65 (43 vs. 22)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Melekos, 1992[77] RCT Medium	A vs. B Age, mean (SD): 66.2 yrs (17) vs. 67.4 yrs (14.3), p > 0.50 Race: NR Sex (male): 83.7% (36/43) vs. 86.4% (31/22), p > 0.80 Smoking status: NR Recurrent bladder cancer: 32.6% (14/43) vs. 31.8% (7/22), p > 0.75 Stage: Ta: 60.5% (26/43) vs. 59.1% (13/22); T1: 39.5% (17/43) vs. 40.1% (9/22); Associated Tis: 4.7% (2/43) vs. 4.5% (1/22); p > 0.75 Grade: G1: 44.2% (19/43) vs. 45.5% (10/22); G2: 44.2% (19/43) vs. 41.0% (9/22); G3: 11.6% (5/43) vs. 13.6% (3/22); p > 0.90 Functional Status: NR Multiplicity: Single: 69.8% (30/43) vs. 72.7% (16/22); Multiple: 30.2% (13/43) vs. 27.3% (6/22); p > 0.90	A vs. B Recurrence: 37.2% (16/43) vs. 54,5% (12/22), p > 0.50 Recurrence-free survival (40 months), A > B, Mantel-Haenszel test, p = 0.11 Relative recurrence rate: 0.81 vs. 1.46, p > 0.05 Recurrence rate/100 patient-months: 1.4 vs. 2.6, p > 0.10 Mean time to recurrence: 18.7 month vs. 12.2 months, p < 0.02 Progression (stage and/or grade): 9.3% (4/43) vs. 22.7% (5/22), p > 0.30	A vs. B Relative risk of recurrence: Primary: 0.84 vs. 1.33, p > 0.50; Recurrent: 0.70 vs. 2.33, p < 0.05 Solitary: 0.87 vs. 1.29, p > 0.50; Multiple: 0.68 vs. 2.32, p ≈ 0.05 Stage: Ta: 0.77 vs. 1.52, p > 0.25; T1: 0.83 vs. 1.45, p > 0.25 Grade: G1: 0.79 vs. 1.49, p > 0.50; G2: 0.81 vs. 1.51, p > 0.25; G3: 0.84 vs. 1.32, p > 0.80 Recurrence rate/100 patient-months: Primary: 0.93 vs. 1.48, p > 0.30; Recurrent: 2.89 vs. 10.53, p < 0.01 Solitary: 1.16 vs. 1.77, p > 0.30; Multiple: 2.18 vs. 7.46, p < 0.03 Stage: Ta: 0.86 vs. 1.78, p > 0.10; T1: 2.82 vs. 4.80, p > 0.20 Grade: G1: 0.80 vs. 1.54, p > 0.30; G2: 1.61 vs. 2.87, p > 0.30; G3: 5.41 vs. 10.34, p > 0.30 Recurrence-free survival: Recurrent tumor, A (n = 14) vs. B (n = 7): A > B, Mantel-Haenszel test, p = 0.018 Multiple tumors, A (n = 13) vs. B (n = 6): A > B, Mantel-Haenszel test, p = 0.05

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1992[77] RCT Medium	NR	NR	Only reported for group A (% patients; % installations) Chemical cystitis, mild: 20.9 %; 8.9% Chemical cystitis, moderate-severe, requiring delay: 7%; 1.2% Macroscopic hematuria: 14%; 3.6% Fever: 2.3%; 0.8% Nausea and vomiting: 2.3%; 0.4% Generalized skin rash: 2.3%; 0.4% No hematological side effects were observed.	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Melekos, 1993[78] RCT Medium	Greece Number of centers not reported Study years not reported	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Multifocal carcinoma in situ and another cancer or history of another cancer outside the bladder and who had had previous local or systemic chemotherapy or radiotherapy	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 ml saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup B. Epirubicin: 50 mg in 50 ml saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup C. TURBT alone	Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter Total months of followup: 1784 vs 1745 vs 603	Screened: Not reported Randomized: 190 (2:2:1) Post-randomization exclusions: 29 patients ineligible due to protocol violation, loss to followup, or other reason Analyzed: 161 (62 vs 67 vs 32)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Melekos, 1993[78] RCT Medium	Age (mean): 67 vs 66 vs 68 years Male: 82% vs 84% vs 84% Race: Not reported Smoking: Not reported Stage: Ta: 66% vs 63% vs 66% T1: 34% vs 37% vs 34% Grade: Grade 1: 44% vs 46% vs 41% Grade 2: 44% vs 37% vs 44% Grade 3: 13% vs 16% vs 16% Tis: 6% vs 4% vs 6%	Recurrence: 32% vs 40% vs 59% Interval before recurrence: 18 months vs 16 months vs 11 months Progression: 6% vs 9% vs 22% Muscle invasion: 3% vs 4% vs 13%	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1993[78] RCT Medium			Withdrawals due to AE: Not reported Cystitis:79% vs 34% vs Not reported Fever: 27% vs 3% vs Not reported Flu-like illness:13% vs 0% vs Not reported Macroscopic hematuria: 23% vs 15% vs Not reported Reduced bladder volume: 0% vs 1% vs Not reported Treatment delay: 5% vs Epi 8% vs Not reported	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	Japan Number sites: 33 Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superfical cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Post-randomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Non-evaluated patients due to protocol violations, cessation of installation, adverse effects, or other reasons. Not quantified overall or by group.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	A vs. B vs. C vs. D Age (yrs), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: Not reported Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR Grade: NR Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * From Akaza, 1987[49]. No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days*: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ Not reported for other treatment group comparisons.	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	A vs. B Recurrence-free survival rate at 540 days: 56.6% vs. 52.0%	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9%	Ministry of Health and Welfare of Japan	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Obata, 1994[79] RCT Medium	Japan Number sites: 62 Study years: July 1985 - June 1987	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G2. Only multiple primary tumors (i.e., solitary primary tumors not included).	Primary and solitary tumor; Residual tumor; Grade G3; Stage T2; Tis; Double cancers; Benign tumor; "Prior treatment within the past 3 weeks".	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 installations over 1 year, after TURBT: Timing of first dose not specified; installations twice a week X 4 weeks, then once a month X 11 months. B: No adjuvant treatment. TURBT alone.	Until January, 1991. Not reported as mean/median nor by group. Method of followup not reported.	Screened: NR Randomized: 544 Postrandomization exclusions: 58 Lost to followup: NR Total Analyzed: 331 Per Group Analyzed (2 groups, A vs. B): 90 vs. 76

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Obata, 1994[79] RCT Medium	A vs. B Age: ≤ 49 years: 11.1% (9/90) vs. 8.0% (3/76); 50-59 years: 15.6% (14/90) vs. 25.0% (19/76); 60-69 years: 40.0% (36/90) vs. 32.9% (25/76); ≥ 70 years: 33.3% (30/90) vs. 34.2% (26/76) Race: NR Sex (male): 77.8% (70/90) vs. 81.6% (62/76) Smoking status: NR Recurrent bladder cancer: 54.4% (49/90) vs. 48.7% (37/76) Stage: Ta: 33.3% (30/90) vs. 43.4% (33/76); T1: 52.2% (47/90) vs. 42.1% (32/76); Tx: 12.2% (11/90) vs. 11.8% (9/76) Grade: G0: 0.0% (0/90) vs. 0.0% (0/76); G1: 31.1% (28/90) vs. 48.7% (37/76); G2: 64.4% (58/90) vs. 46.1% (35/76); Gx: 3.3% (3/90) vs. 3.9% (3/76) Functional Status: NR Size: < 1 cm: 51.1% (46/90) vs. 57.9% (44/76); 1-3 cm: 36.7% (33/90) vs. 32.9% (25/76); > 3 cm: 8.9% (8/90) vs. 5.7% (4/76); Unknown: 3.3% (3/90) vs. 3.9% (3/76) Multiplicity: Single: 16.7% (15/90) vs. 11.8% (9/76); 2-4: 56.7% (51/90) vs. 68.4% (52/76); ≥ 5: 24.4% (22/90) vs. 18.4% (14/76); Unknown: 1.1% (1/90) vs. 1.3% (1/76) (Statistical testing only reported for all 4 groups combined, not for A vs. B)	A vs. B Recurrence-free survival rate at 3 years: 44% vs. 30% (Statistical testing only reported for all 4 groups combined, not for A vs. B)	A vs. B Recurrence-free survival rate at 3 years: Primary tumor: 47% vs. 37% Recurrent tumor: 41% vs. 23% Risk ratio (B as reference): Primary-multiple: 0.81 Recurrent-solitary: 1.09 Recurrent-multiple: 0.40 (Statistical testing only reported for all 4 groups combined, not for A vs. B)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Obata, 1994[79] RCT Medium	NR	NR	Reported for A only Pollakiuria: 18.9% (17/90) Pain on urination: 22.2% (20/90) Dysuria: 4.4% (4/90) Hematuria: 12.2% (11/90) Contracted bladder: 1.1% (1/90)	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Okamura, 2002[80] RCT Medium	Japan Number sites: NR (Authors from multiple centers) Study years: May 1994 - July 1998	Superficial bladder carcinoma that could be resected transurethrally (primary or recurrent). Solitary; smaller than 30 mm. Stages Ta or T1; Grade G1 or G2.	No recurrence within 1 year prior to enrollment. Eastern Cooperative Oncology Group performance status > 2; age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Doxorubicin [(2' ' R)-4'-0-Tetrahydropyranyl-Doxorubicin)], 30 mg (in 30 ml normal saline). Single intravesical installation within 6 hours of TURBT; retained in bladder for 1 hour. B: No adjuvant treatment. TURBT alone.	Median followup (Overall; not reported by groups): 40.8 months. Cystoscopy and urinary cytology every 3 months X 2 years. Then, cystoscopy every 6 months X 3, and "1 year after that". Patients were monitored for local and systemic side toxicities.	Screened: NR Randomized: 170 (84 vs. 86) Postrandomization exclusions: none Lost to followup: None Total Analyzed: 160 (81 vs. 79)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Okamura, 2002[80] RCT Medium	A vs. B Age, mean: 59.7 ± 11.7 (range, 23-82) vs. 61.9 ± 11.6 (range, 28-82) Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer: 7.4% (6/81) vs. 2.5% (2/79) Stage: pTa: 95.1% (77/81) vs. 93.7% (74/79); pT1: 4.9% (4/81) vs. 6.3% (5/79) Grade: G1: 50.6% (41/81) vs. 45.6% (36/79); G2: 46.9% (38/81) vs. 49.4% (39/79); G3: 2.5% (2/81) vs. 5.1% (4/79) Functional Status: All patients had Eastern Cooperative Oncology Group performance status ≤ 2 "There was no significant difference in patient characteristics between the 2 groups".	A vs. B Recurrence-free survival: A > B, p = 0.0026 Mean interval to initial recurrence, months: 41.9 vs. 18.0 Net benefit for recurrence at 1 year: 25.4% Net benefit for recurrence at 2 years: 27.0% Net benefit for recurrence at 3 years: 21.5% Recurrence rate per year: 0.11 ± 0.22 vs. 0.24 ± 0.36, p = 0.007 HR (adjust; covariates not specified) for recurrence for A (B as reference): 0.31 (95% CI: 0.17-0.56, p = 0.0001)	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Okamura, 2002[80] RCT Medium	NR	NR	Only local toxicities observed; No severe local toxicities encountered. Adverse events only reported for Group A: Dysuria : 10.7% (9/84) Urinary frequency/urgency: 6.0% (5/84) Macroscopic hematuria: 8.3% (7/84)	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Oosterlinck, 1993[81] RCT Medium	Europe (multinational) Number sites: 36 Study years: October 1986 - October 1989	Biopsy-proved, papillary transitional cell carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3. Single tumor.	Stage Tis; WHO performance status > 2; Age > 85 years; Uncontrollable UTI; Previously treated with chemotherapy within previous 12 months.	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single installation within 6 hours after TURBT. Catheter clamped X 1 hour, then irrigated with normal saline X 24 hours. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3. B: Placebo. Sterile water, 50 mL. Single installation within 6 hours after TURBT. Catheter clamped X 1 hour, then irrigated with normal saline X 24 hours. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3.	2 years (average), overall. 4.5 years (maximum), overall. Cystoscopy, urine cytology, urinalysis; first followup cystoscopy 4 weeks after TURBT, then every 3 months for year 1, then every 4 months for year 2, then every 6 months thereafter. For recurrence on followup cystoscopy, patients had repeat TURBT and repeat of original installation for each recurrence until maximum of 3. Patients excluded after 3 recurrences, multiple recurrent tumors, stage Tis, increase in stage greater than T1, or distant metastases.	Screened: NR Randomized: 512 (257 vs. 255) Postrandomization exclusions: 11 Lost to followup: 21 Total Analyzed: Baseline: 420 (205 vs. 215); followup: 399 (194 vs. 205)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Oosterlinck, 1993[81] RCT Medium	A vs. B (205 vs. 215) Age: Not reported ("comparable in the 2 treatment groups", no p-value) Race: Not reported % Male: Not reported ("comparable in the 2 treatment groups", no p-value) Smoking status: Not reported Recurrent bladder cancer: 21.0% (43/205) vs. 23.0% (49/215) Stage: pTa: 70.7% (145/205) vs. 76.7% (165/215); pT1: 29.3% (60/205) vs. 23.0% (49/215); Unknown: 0.0% (0/205) vs. 0.5% (1/215) Grade: G1: 38.0% (78/205) vs. 50.7% (109/215); G2: 47.8% (98/205) vs. 40.9% (88/215); G3: 11.7% (24/205) vs. 7.0% (15/215); Gx: 2.4% (5/205) vs. 1.4% (3/215) Functional Status: Not reported Size: < 1 cm: 26.3% (54/205) vs. 30.2% (65/215); < 3 cm: 58.5% (120/205) vs. 54.0% (116/215); > 3 cm: 11.7% (24/205) vs. 13.9% (29/215); Unknown: 3.4% (7/205) vs. 2.3% (5/215)	A vs. B Recurrence: 29% (56/194) vs. 41% (84/205), log-rank test, p = 0.02 Recurrence rate/year: 0.17 vs. 0.32, p < 0.0001 Progression: 8.8% (17/194) vs. 7.3% (15/205), "no evidence of difference", p-value not reported.	A vs. B Recurrence rate: Primary tumor: 0.15 vs. 0.31, p < 0.0001; Recurrent tumor: 0.26 vs. 0.35, p = 0.38.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Oosterlinck, 1993[81] RCT Medium	NR	NR	A vs. B (205 vs. 215), followup duration not clear. Chemical cystitis: 11.7% (24/205) vs. 1.9% (4/215) Skin allergy: 1.0% (2/205) vs. 0.0% (0/215) Other: 3.4% (7/205) vs. 0.9% (2/215) No hematological toxicity noted at 8 days after TURBT. No serious or long-lasting side effects were noted.	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Pagano, 1991[82] RCT High Preliminary results Pagano, 1990[83] RCT High	Italy Single Center 1986-1988	Patients followed for one year after the study or until recurrence or progression were included in the report. Multiple (>3 tumors at entry), superficial papillary and nonpapillary tumors	NR	A. TURBT+BCG 75 mg (Pasteur strain) in 50 ml saline, 6 weekly instillations, if recurrence without progression then additional 6 week course of BCG, maintenance monthly instillations for 1 year and then quarterly for one year B. TURBT alone	Mean followup period 21 months	Screened: not reported Randomized: 189 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 133 (70 vs 63)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Pagano, 1991[82] RCT High Preliminary results Pagano, 1990[83] RCT High	Age (mean): 57 years Male: 91% Race: Not reported Smoking: Not reported	Complete responses Complete response: 52(74%) vs 11 (17%) Progression: 3 (4%) vs 11 (17%) Recurrence rate: 4% vs 12%	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pagano, 1991[82] RCT High Preliminary results Pagano, 1990[83] RCT High			NR	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Palou, 2001[84] RCT Medium	Spain, England Number of centers not reported 1989-1995	Primary or relapsing stage Ta or T1 grade 3 superficial bladder tumors with or without associated CIS or isolated CIS or associated with grade 2 superficial bladder tumors	Invasive bladder tumors, bladder radiotherapy, intolerance to the first course of BCG instillations	Initial treatment with 6 weekly instillations of BCG 81 mg (Connaught strain); if relapse then 6 additional weekly instillations; if disease free then randomized to: A. BCG 81 mg (Connaught) 6 weekly instillations every 6 months for 2 years B. No further treatment After randomization, high grade superficial relapse treated with new course of BCG instillations; low grade relapses treated with MMC or BCG	Alternating cytology and cystoscopy every 3 months for 2 years and then cytology and cystoscopy every 6 months Median followup 78 months	Screened: Not reported Randomized: 131 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 126 (65 vs 61)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Palou, 2001[84] RCT Medium	Age (mean) 65 vs 63 Male: 98% vs 92% Race: Not reported Smoking: Not reported Stage: Ta: 22 (34%) vs 19 (31%) T1: 31 (48%) vs 34 (56%) Solitary CIS: 12 (18%) vs 8 (13%)	Tumor-free: 53 vs 46 Superficial relapse: 10 (15%) vs 16 (26%), p=0.07 Progression: 3 vs 2 Mortality: 11 vs 8 Died of bladder cancer: 3 vs 2	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Palou, 2001[84] RCT Medium			Discontinued installations due to side effects: 32 in BCG maintenance group; number in control group not reported	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Portillo, 1997[85] RCT Medium	Spain Number sites: NR (authors from single center) Study years: July 1990 - January 1994	Completely resected transitional cell carcinoma of the bladder (primary and recurrent). Stage pT1; Grades G1, G2 or G3. (G1 recurrent only). Life expectancy > 1 year.	Stage Ta tumor; G1 primary tumor; History of any other tumors (except nonmelanoma cutaneous tumors); Refractory urinary infection; Urethral stenosis.	A: Interferon-α-2b, 60 million units. B: Placebo (double distilled water). A and B: First installation 2-3 weeks after TURBT; Once weekly X 12 weeks, then once monthly X 9 months (Total: 21 installations over 1 year).	Mean followup (Overall; not reported by groups): 43months (range 9 to 67 months). Cystoscopy, urinary cytology, laboratory blood tests (hemogram and biochemical analysis), urine test, urine culture, every 3 months X 1 year, then every 4 months X 1 year, then every 6 months thereafter. Also, occasional ultrasound or urography. After first relapse, patients were switched to intracavitary BCG, 81 mg weekly X 6.	Screened: NR Randomized: 90 Postrandomization exclusions: NR Lost to followup: 12 Total Analyzed: 78 (39 vs. 39)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Portillo, 1997[85] RCT Medium	A vs. B Age, mean: 64.9 years, overall (not reported by group) Race: NR Sex (male): 87.2% (68/78), overall (not reported by group) Smoking status: NR Recurrent bladder cancer: 19.1%, overall (not reported by group, p = NS) Stage and Grade: T1G1: 2.6% (1/39) vs. 12.8% (5/39); T1G2: 82.1% (32/39) vs. 61.5% (24/39); T1G3: 15.4% (6/39) vs. 25.6% (10/39); p = NS Functional Status: NR Multiplicity: Single tumor: 60.0% (23/39) vs. 69.2% (27/39); 2-3 tumors: 10.3% (4/39) vs. 20.5% (8/39); > 3 tumors: 30.8% (12/39) vs. 10.3% (4/39); p = NS.	A vs. B Recurrence at 12 months: 28.2% (11/39) vs. 35.9% (14/39) Recurrence at mean followup of 43 months: 53.8% (21/39) vs. 51.3% (20/39), p = NS. Recurrence-free interval: 17 months vs. 9.6 months, p = NS Progression (stage, grade, diffuse CIS, and/or metastasis): 7.7% (3/39) vs. 17.9% (7/39), p = NS Mortality due to bladder cancer: 5.1% (2/39) vs. 5.1% (2/39), p = NS	"A comparison of relapses according to histologic grades and treatment groups revealed no statistically significant difference between the groups (p = NS)"

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Portillo, 1997[85] RCT Medium	NR	NR	A vs. B UTI: 23.3% vs. 16.7%, p = NS "Analytical changes" (hypercholesterolemia, hyperuricemia): 6.7% vs. 13.3%, p = NS "There were no reports of flu-like syndrome."	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	Finland Number sites: 18 Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 million units (in 100 ml physiological saline). Single intravesical installation immediately after TURBT, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 ml physiological saline). Single intravesical installation immediately after TURBT, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.	Overall duration of study was 2 years. Mean/median followup durations not reported. Cystoscopy and urinary cytology every 3 months X 2 years.	Screened: 283 Randomized: 283 Postrandomization exclusions: 40 Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	A vs. B vs. C Age: NR Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)	A vs. B vs. C Recurrence: 63.7% (42/66) vs. 33.8% (23/68) vs. 60.6 (40/66)	A vs. B vs. C Recurrence by stage: Ta: 64.2% (34/53) vs. 35.2% (19/54) vs. 56.4% (31/55), p < 0.05 T1: 61.5% (8/13) vs. 28.6% (4/14) vs. 81.8% (9/11), p < 0.01 Recurrence by grade: G1: 51.7% (15/29) vs. 20.6% (7/34) vs. 52.6% (20/38), p < 0.01 G2: 70.0% (20/29) vs. 44.0% (11/25) vs. 66.7% (14/21), p = 0.09 G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7), p = NS Recurrence by tumor multiplicity: Single: 62.7% (32/51) vs. 26.9% (14/52) vs. 55.3% (26/47), p < 0.01 Multiple: 66.7% (10/15) vs. 56.3% (9/16) vs. 73.7% (14/19), p = NS

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	NR	NR	A vs. B vs. C Fever: 6% (4/66) vs. 0% (0/68) vs. 1.5% (1/66) Dysuria: 1.5% (1/66) vs. 5.9% (4/68) vs. 0% (0/66)	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	Finland Number sites: 18 Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 milliunits (in 100 ml physiological saline). Single intravesical installation immediately after TURBT, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 ml physiological saline). Single intravesical installation immediately after TURBT, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.	Median followup (Overall; not reported by groups): 72 months (range 6-102). Cystoscopy and urinary cytology every 3 months X 1 year. Thereafter, followup cystoscopy according to the practice at each center.	Screened: 283 Randomized: 283 [see comment] Postrandomization exclusions: 40 [see comment] Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	A vs. B vs. C Age, mean: 66.3 vs. 65.1 vs. 64.6 Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)	A vs. B vs. C Recurrence: 68.2% (45/66) vs. 45.6% (31/68) vs. 72.7 (48/66), p = 0.002 Recurrence-free at 72 months: 31.4% vs. 50.8% vs. 23.7% Recurrence-free survival: B > A or C, p = 0.002 Median time to first recurrence, months (95% CI): 12 (9-15) vs. [not attained] vs. 9 (5-13)	A vs. B vs. C Recurrence by stage: Ta: 67.9% (36/53) vs. 46.3% (25/54) vs. 70.9% (39/55) T1: 69.2% (9/13) vs. 42.9% (6/14) vs. 81.8% (9/11) Recurrence by grade: G1: 58.6% (17/29) vs. 38.2% (13/34) vs. 65.8% (25/38) G2: 72.4% (21/29) vs. 52.0% (13/25) vs. 81.0% (17/21) G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7) Recurrence by tumor multiplicity: Single: 64.7% (33/51) vs. 42.3% (22/52) vs. 70.2% (33/47) 2 tumors: 70.0% (7/10) vs. 33.3% (3/9) vs. 83.3% (10/12) 3 tumors: 100% (3/3) vs. 80.0% (4/5) vs. 33.3% (1/3) ≥ 4 tumors: 100% (2/2) vs. 100% (2/2) vs. 100% (4/4)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	NR	NR	NR	Finnish Cancer Foundation; Pharmacia; Roche and Schering-Plough	Study is followup of Rajala, 1999. Description of followup cystoscopy internal after year 1 is not consistent with Rajala, 1999. Number randomized and postrandomization exclusion taken from Rajala, 1999.

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Saika, 2010[88] RCT Medium	Japan Number of sites: 25 Study years: April 1995 - January 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥ 20 years.	Concurrent or previous CIS; Concurrent or previous urinary tract cancer; Concurrent or previous muscle invasive disease; Lethal disease.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (< 1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.	A vs. B vs. C Median followup, overall: 44 months (range 1-70 months) Median followup, months, by group: 44 vs. 46 vs. 42 Cystoscopy every 3 months for 2 years and every 6 months thereafter.	Screened: NR Randomized: 303 Postrandomization exclusions: 21 Eligible: 257 (83 vs. 90 vs. 84) Lost to followup: 17 Total analyzed: 240 (79 vs. 84 vs. 77)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Saika, 2010[88] RCT Medium	A vs. B vs. C (based on eligible patents, n = 257) Median age, years: 69 vs. 69 vs. 71 Sex (male): 81% (67/83) vs. 89% (80/90) vs. 88% (74/84) Race: NR Recurrent bladder cancer: 40% (33/83) vs. 43% (39/90) vs. 40% (34/84) Stage Ta: 54% (45/83) vs. 60% (54/90) vs. 64% (54/84) Stage T1: 46% (36/83) vs. 40% (36/90) vs. 36% (30/84) Grade G1: 25% (21/83) vs. 33% (30/90) vs. 31% (26/84) Grade G2: 59% (49/83) vs. 47% (42/90) vs. 52% (44/84) Grade G3: 14% (12/83) vs. 20% (18/90) vs. 17% (14/84) Functional status: NR	A vs. B vs. C Median recurrence-free survival, months: 24 vs. 38 vs. 13; A vs. B, p = 0.48; A vs. C, p=0.25; B vs. C, p=0.05 Progression: 0.0% (0/83) vs. 1.1% (1/90) vs. 0.0% (0/84)	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Saika, 2010[88] RCT Medium	NR	NR	A vs. B (not reported for group C) Local: Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p = 0.106 Systemic: Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Solsona, 1999[89] RCT Medium	Spain Number sites: NR (authors from single center) Study years: January 1988 - August 1992	Low risk superficial bladder cancer. Primary or recurrent (disease-free for more than 1 year); Stages Ta or T1; Grade G1 or G2; Single tumor ≤ 3 cm; Papillary; Upper urinary tract normal on excretory urography.	Muscle -invasive; Grade G3; CIS; WHO performance status > 2; Age > 80 years; Uncontrolled UTIs; Psychological disturbances.	A: Mitomycin C, 30 mg (in 50 mL saline). Single intravesical dose; installed when hematuria ceased, usually within 6 hours of TURBT; Retained in bladder for 1 hour with catheter clamping; bladder then irrigated with saline. B: No adjuvant therapy. TURBT only.	A vs. B Median followup, months: 94 vs. 93 Urinary cytology and cystoscopy at 3, 6, 9, 12, 18, and 24 months; and then once per year. At 15 and 21 months, urinary cytology and bladder ultrasound, intercalated with annual endoscopic evaluations.	Screened: NR Randomized: 131 Postrandomization exclusions: none Lost to followup: 3 Total analyzed: 121 (57 vs. 64)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Stavropoulos, 2002[90] RCT Medium	Greece Number of sites: NR (authors from 3 centers) Study years: NR	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G2 or G3. Of patients with TaG2 tumors, only those with recurrent and/or multiple tumors were included.	Concomitant carcinoma in situ; History of another neoplasia elsewhere in the body; Previously treated with any form of intravesical instillations.	A. Interferon-γ, 21 MU (in 50 mL physiological saline) per week for 8 weeks, retained in the bladder for 2 hours. B. No adjuvant treatment. TURBT alone.	followup: Mean: 12.1 months; Median: 9 months; Range: 3-40 months. (Not reported for each group separately). Cystoscopy every 3 months for 15 months and every 6 months thereafter. Freedom of recurrence established cystoscopically and cytologically.	Screened; NR Randomized: 60 Postrandomization exclusions: none Lost to followup: 6 (4 vs. 2) Total analyzed: 54 (26 vs. 28)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Solsona, 1999[89] RCT Medium	A vs. B Age, mean (years): 62.2 vs. 59.9 Race: NR Sex (male): 91.2% (52/57) vs. 92.2% (59/64) Smoking status: NR Recurrent bladder cancer: 10.5% (6/57) vs. 12.5% (8/64) Stage Ta: 49.1% (28/57) vs. 48.4% (31/64) Stage T1: 50.9% (29/57) vs. 51.6% (33/64) Grade G1: 52.6% (30/57) vs. 51.6% (33/64) Grade G2: 47.4% (27/57) vs. 48.4% (31/64) All patients with WHO performance status ≤ 2.	A vs. B Recurrence: Early (during first 2 years followup): 15.8% (9/57) vs. 34.4% (22/64), p = 0.019 Late (after 2 years followup): 22.8% (13/57) vs. 21.9% (14/64), p = 0.575 Early + Late: 10.5% (6/57) vs. 12.5% (8/64), p = 0.734 Overall: 40.4% (23/57) vs. 54.7% (35/64), p = 0.115 Recurrence free at 24 months: 84.2% vs. 65.6%; log-rank test for early recurrence-free, p = 0.013 Recurrence free at 108 months: 57.0% vs. 42.2%; log-rank test for overall recurrence-free, p = 0.057 Progression: 1.8% (1/57) vs. 1.6% (1/64)	NR

Stavropoulos, 2002[90] RCT Medium	A vs. B Mean age: 66 vs. 64 years Male sex: 88% (23/26) vs. 71% (20/28) Race: NR Smoking status: NR Recurrent bladder cancer: 27% (7/26) vs. 29% (8/28) Stage Ta: 42% (11/26) vs. 64% (18/28) Stage T1: 58% (15/26) vs. 36% (10/28) Grade G2: 58% (15/26) vs. 57% (16/28) Grade G3: 42% (11/26) vs. 43% (12/28) Functional status: NR	A vs. B Recurrence: 61.5% (16/26) vs. 85.7% (24/28); p=0.043 Median time to first recurrence:12.0 months vs. 7.5 months Disease-free survival, median months (95% CI): 12.0 (8.3-15.7) vs. 7.0 (4.4-9.6); log-rank test, p = 0.024. Progression to muscle-invasive disease: 3.8% (1/26) vs. 3.6% (1/28).	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Solsona, 1999[89] RCT Medium	NR	NR	Group A: Two patients (3.5%) had chemical cystitis and slight allergic skin reactions. Group B: One patient (1.6%) had cystitis with negative urine culture. No hematological changes were noted.	NR	

Stavropoulos, 2002[90] RCT Medium	NR	NR	"Apart from transient and mild irritative voiding symptoms, no significant side effects were noted"	NR	

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)
Tolley, 1996[91] RCT Medium (followup of Tolley, 1988[92])	United Kingdom Number of sites: 17 Study years: March 1984 - December 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 - 3.	CIS alone	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes. B: Mitomycin C 40 mg (in 40 mL water), installation within 24 hours of TURBT; retained for 60 minutes. Additional installations (same dose) every 3 months x 1 year (total 5 installations). C: No adjuvant treatment. TURBT alone.	Median followup (A and B, not reported for C): 7 years Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: 502 Randomized: 452 Postrandomization exclusions: NR Lost to followup: 5* (2 vs. 1 vs. 2) Total analyzed: 452 (149 vs. 146 vs. 157) * reportedly with no followup data, but included in ITT analyses

AE, Adverse Events; ALT, Alanine transaminase; AST, Aspartate transaminase; BCG, Bacillus Calmette Guerin; CBC, Complete blood count; cc, cubic centimeter; CFU, Colony Forming Unit; CIS, carcinoma in situ; cm, centimeter; CRR, Cumulative recurrence rate; DNA, Deoxyribonucleic acid; ECG, electrocardiography; Epi, Epirubicin; g/dL, gram per deciliter; G0, Grade 0; G1, Grade 1; G2, Grade 2; G3, Grade 3; GEM, Gemcitabine; Gx, Grade unknown; Hgb, Hemoglobin; hr, hour; IFN-a-2b, Interferon alpha 2b; IQR, Inter quartile range; ITT, intention-to-treat analysis; IVU, intravenous urogram; L, Liter; mg, milligram; mg/dL, milligram per deciliter; MIBC, Muscle Invasive Bladder Cancer; ml, milliliter; mL, milliliter; MMC, Mitomycin C; MU, Million units; NA, Not applicable; NaCl, Sodium Chloride; NMICB, Non-Muscle Invasive Bladder Cancer; NR, Not Reported; NS, Not significant; PBO, Placebo; PPD, purified protein derivative; pT1, Tumor stage 1 determined by pathology; pT1b, Tumor stage 1b determined by pathology; pT2, Tumor stage 2 determined by pathology; pTa, Tumor stage 3 determined by pathology; pTa/1, Tumor stage a determined by pathology; pTis, Tumor in situ determined by pathology; RCT, Randomized Controlled Trial; RFS, Recurrence free survival; SD, Standard deviation; SWOG, Southwest Oncology Group; T1, Tumor stage 1; Ta, Tumor stage a; TCC, Transitional cell carcinoma; Tis, carcinoma in situ; TUR, Transurethral resection; TURBT, Transurethral resection of bladder tumour; USA, United States of America; UTIs, Urinary Tract Infections; WBS, White blood cells; WHO, World Health Organization; yr(s), year(s)

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Tolley, 1996[91] RCT Medium (followup of Tolley, 1988[92])	A vs. B vs. C Age 24-50: 13% (19/149) vs. 9% (13/146) vs. 9% (14/157) Age 51-60: 24% (36/149) vs. 23% (33/146) vs. 29% (46/157) Age 61-70: 36% (54/149) vs. 37% (54/146) vs. 34% (53/157) Age 71-80: 23% (34/149) vs. 30% (44/146) vs. 25% (40/157) Age 81-100: 4% (6/149) vs. 1% (2/146) vs. 3% (2/157) Male sex: NR Race: NR Smoking status: NR Stage Ta: 50% (75/149) vs. 52% (76/146) vs. 56% (88/157) Stage T1: 48% (72/149) vs. 50% (73/146) vs. 43% (67/157) Grade 1: 37% (55/149) vs. 34% (50/146) vs. 45% (71/157) Grade 2: 52% (77/149) vs. 55% (81/146) vs. 46% (73/157) Grade 3: 10% (15/149) vs. 10% (15/146) vs. 8% (13/157) Functional status: NR	A vs. B vs. C Annual recurrence rate (positive cystoscopies) during first 2 years: 0.42 vs. 0.31 vs. 0.82; A vs. C, p=0.001; B vs. C, p<0.001; A vs. B, p = 0.14 Recurrence, relative risk, HR (95% CI): A vs. C (ref): 0.66 (0.48 to 0.91), log-rank test, p = 0.01; B vs. C (ref): 0.50 (0.36 to 0.70), log-rank test, p = 0.0001; A vs. B (ref): 0.74 (0.51 to 1.06), log-rank test, p = 0.10 Progression, relative risk, HR (95% CI): A vs. C: 0.84 (0.42 to 1.52), log-rank test, p = 0.64; B vs. C: 0.82 (0.40 to 1.68), log-rank test, p = 0.59; A vs. B: 0.97 (0.46 to 2.06), log-rank test, p = 0.94 All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146) vs. 32.5% (51/157); A+B vs. C, HR 1.1 (95% CI 0.80 to 1.53) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146) vs. 7.6% (12/157)	NR

Appendix E2. Key Question 3: Intravesical Compared With No Intravesical

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Tolley, 1996[91] RCT Medium (followup of Tolley, 1988[92])	NR	NR	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was not reported as a side effect by any patient in either group.	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Addeo, 2010[93] RCT Medium	Italy Number sites: Unclear (authors from 4 centers) Study years (enrollment): March 2003 - November 2005	Recurrent transitional cell carcinoma. Stages Ta or T1; any grade (1, 2, or 3). Progression or relapse after intravesical BCG; Ineligible for BCG	Prior pelvic irradiation; intractable UTIs	A: Mitomycin (MMC), 40 mg (in 50 mL normal saline) intravesical; first infusion within 2 days after TURBT, then 4 weekly treatments. B: Gemcitabine (GEM), 2,000 mg (in 50 mL normal saline) intravesical; "6-week induction course of infusion", dosing not otherwise specified. A and B: Maintenance therapy of 10 monthly treatments for initial responders who remained free of recurrence. Oral antibiotics for 2 days after each infusion.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Addeo, 2010[93] RCT Medium	Median: 36 months for each group	Screened: NR Randomized: 120 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 109 Per Group Analyzed: A: 55; B: 54	A vs. B Age (yrs), mean (SD): 67.9 (10.2) vs. 64.9 (SD 10.55) Age (yrs), median: 70 vs. 66.5 Sex (male): 85.5% (47/55) vs. 85.2% (46/54) Race: Not reported Smoking status: NR Recurrent bladder cancer: 100% (34/55, single; 21/55, multiple) vs.100% (29/54, single; 25/54, multiple) Stage: Ta: 63.6% (35/55) vs.68.5% (37/54); T1: 36.4% (20/55) vs. 31.5% (17/54) Grade: G1: 25.5% (14/55) vs. 20.4% (11/54); G2: 49.1% (27/55) vs. 51.9% (28/54); G3: 25.5% (14/55) vs. 27.8% (15/54) Functional Status: NR Previous treatment: A: BCG: 45/55, Epirubicin: 10/55; B: BCG: 46/54, Epirubicin: 8/54

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Addeo, 2010[93] RCT Medium	Median time to recurrence: A: 15.0 months; B: "Not reached" Relative risk of recurrence: A: 0.94; B: 0.72; p = 0.291 Recurrence rate/100 patient-months: A: 1.72; B: 1.26; p =0.31 Patients with tumor progression by stage: A: 10; B: 6; p =0.14 Probability of disease-free survival over time (Kaplan-Meier curve): GEM > MMC; p = 0.0021	Probability of disease-free survival over time for grade 3 neoplasms (Kaplan-Meier curve): GEM > MMC; p = 0.049 No differences in G1, G2, T1 or number of tumors between the two treatment arms.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Addeo, 2010[93] RCT Medium	NR	NR	Withdrawals due to AE: NR precisely, though between 1 and 4 Dysuria, n (%): A: 11 (20%); B: 5 (9.2%); p = 0.023 Suprapubic pain, n (%): A: 4 (7.2%); B: 6 (11%); p = 0.949 Hematuria, n (%): A: 4 (7.2%); B: 2 (3.7%); p = 0.601 Chemical cystitis, n (%): A: 12 (21.1%); B: 3 (5.5%); p = 0.013 Local reactions, n (%): A: 5 (9%); B: 2 (3.7%); p = 0.465 Skin reaction, n (%): A: 6 (10.9%); B: 3 (5.5%); p = 0.505 Total, n (%): A: 40 (72.2%); B: 21 (38.8%); p = 0.021	Lega Italiana per la Lotta contro I Tumori; Financial support by two of the authors	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	Japan Number sites: 33 Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Non-evaluated patients due to protocol violations, cessation of installation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (yrs), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: Not reported Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.05 Not reported for other treatment group comparisons. roup comparisons.	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.01 Comparisons not reported for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as non-significant, no p - values reported.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987[49] RCTs (2 studies) Study One (followup of Niijima, 1983[50]) Medium	A vs. B Recurrence-free survival rate at 540 days: 56.6% vs. 52.0%	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	Japan Number sites: Unclear Study years: July 1982 - 1985	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	3.5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148)	A vs. B vs. C vs. D Age (yrs), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Sex (male): 80.1% (121/151) vs. 82.3% (130/158) vs. 82.0% (123/150) vs. 81.1% (120/148) Race: Not reported Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 31.8% (48/151) vs. 30.4% (48/158) vs. 36.0% (54/150) vs. 38.5% (57/148); 1-3 cm: 51.0% (77/151) vs. 53.2% (84/158) vs. 44.0% (66/150) vs. 49.3% (73/148); 3-5 cm: 14.6% (22/151) vs. 11.4% (18/158) vs. 11.3% (17/150) vs. 6.8% (10/148) Number of tumors: 1: 64.2% (97/151) vs. 55.7% (88/158) vs. 55.3% (83/150) vs. 66.9% (99/148); 2-4: 29.8% (45/151) vs. 30.4% (48/158) vs. 33.3% (50/150) vs. 23.6% (35/148); 5+: 6.0% (9/151) vs. 12.7% (20/158) vs. 10.7% (16/150) vs. 8.1% (12/148) * No data provided on stage or grade, but reported "absolutely no intergroup differences were found".

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0% vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1% vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, $p < 0.05$ B > D, $p < 0.05$ C > D, $p < 0.05$ Not reported for other treatment group comparisons.	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987[49] RCTs (2 studies) Study Two Medium	A vs. B Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 Recurrence-free survival rate at 2 years: 62.3% vs. 59.1	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	Japan Number sites: Unclear Study years: July 1982 - May 1990	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	Median, overall: 2,366 days (6.5 years); range: 480-2,817 days. Not reported for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: 671 Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: 134 Total Analyzed: 158 Per Group Analyzed: (44 vs. 42 vs. 41 vs. 31)	Only reported overall; Not reported by treatment group Age ≤ 50 years: 13.3% (21/158) Age ≤ 60 years: 17.7% (28/158) Age < 70 years: 35.4% (56/158) Age ≥ 70 years: 33.5% (53/158) Sex (male): 84.8% (134/158) Race: NR Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: Tis: 1.3% (2/158); Ta: 44.3% (70/158); T1: 40.5% (64/158); Ta or T1: 13.9% (22/158) Grade: G1: 48.7% (77/158); G2: 45.6% (72/158); G1 or G2: 5.7% (9/158) Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	A vs. B vs. C vs. D Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31), "Statistics: no difference"	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1992[51] RCT Study Two (followup of sub-group of Akaza, 1987[49]) High	A vs. B Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42)	NR	NR	Ministry of Health and Welfare of Japan	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	Egypt Number sites: 1 Study years: January 1992 - February 1996	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages pTa or pT1, confirmed histologically; Grade G1 - G3. Multiplicity; Patients with pTa were included if they had multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function; CIS.	A: Epirubicin, 50 mg (in 50 ml normal saline); Single installation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 ml normal saline); Initial installation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, installations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	16 to 49 months (mean 32.2, SD 11.4); Not reported for each group separately. Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years. Annual IVU. Urinalysis, urine culture, full blood count, and ECG before each installation.	Screened: 181 Randomized: 179 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 168 Per Group Analyzed (A vs. B vs. C): 55 vs. 59 vs. 54	A vs. B vs. C Age, mean years (range): 52.1 (36-65) vs. 55 (30-68) vs. 53.4 (32-72) Race: NR Sex (male): 67.3% (37/55) vs. 74.6% (44/59) vs. 70.4% (38/54) Smoking status: NR Recurrent bladder cancer: 47.2% (26/55) vs. 52.5% (31/59) vs. 44.4% (24/54), p = 0.5 Stage: pTa: 16.3% (9/55) vs. 25.4% (15/59) vs. 18.5% (10/54); pT1: 83.7% (46/55) vs. 74.6% (44/59) vs. 81.5% (44/54), p = 0.4. Grade: G1: 10.9% (6/55) vs. 18.6% (11/59) vs. 25.9% (14/54); G2: 54.5% (30/55) vs. 55.9% (33/59) vs. 53.7% (29/54); G3: 34.5% (19/55) vs. 25.4% (15/59) vs. 20.4% (11/54), p = 0.2. Functional Status: NR Size: < 3 cm: 65% (36/55) vs. 71% (42/59) vs. 63% (34/54); ≥ 3 cm: 35% (19/55) vs. 29% (17/59) vs. 37% (20/54)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B vs. C Recurrence: 23.6% (13/55) vs. 25.4% (15/59) vs. 51.8% (28/54), A vs. B vs. C, p = 0.002, A and B vs. C, p < 0.001, A vs. B, p = 0.8. Mean interval to first recurrence, months: 16 vs. 18 vs. 6.9, p < 0.05. Recurrence rate per 100 patient-months: 0.79 vs. 0.84 vs. 2.01 Progression: 5.5% (3/55) vs. 3.4% (2/59) vs. 9.3% (5/54), p = 0.4.	A vs. B (No data for group C) Simple recurrence rate according to stage: Ta: 0.0% (0/9) vs. 0.0% (0/15); T1: 28.3% (13/46) vs. 34.1% (15/44), p = 0.7. Simple recurrence rate according to grade: G1: 0.0% (0/6) vs. 27.3% (3/11); G2: 10.0% (3/30) vs. 27.3% (9/33), p = 0.3; G3: 52.6% (10/19) vs. 20.0% (3/15), p = 0.05. Simple recurrence rate for large tumors (≥ 3 cm in greatest dimension): 21.1% (4/19) vs. 41.2% (7/17), p =0.5.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B Simple recurrence rate: 23.6% (13/55) vs. 25.4% (15/59), p = 0.8. Mean interval to first recurrence, months: 16 vs. 18 Recurrence rate per 100 patient-months: 0.79 vs. 0.84 Progression: 5.5% (3/55) vs. 3.4% (2/59)	NR	A vs. B (No data for group C) Proportion of patients with an adverse event: 21.8% (12/55) vs. 25.4% (15/59), p = 0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15) , p = 0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p = 0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.	No financial support received	Note: Possible overlap of some study subjects (group B) with those in Ali-El-Dein, 1997 (J Urol)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	Egypt Number sites: 1 Study years: June 1991 - May 1995	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function.	A: Epirubicin, 50 mg (in 50 ml normal saline). B: Epirubicin, 80 mg (in 50 ml normal saline). C: Doxorubicin, 50 mg (in 50 ml normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First installation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Installations once a week X 8 weeks, then once monthly to complete 1 year of treatment.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	12 to 48 months (mean 30.1 months); Not reported for each group separately. Cysto-urethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter. Excretory urography every year. Urinalysis, urine culture, serum creatinine, CBC, ECG, and urine pH before and after each installation.	Screened: NR Randomized: 253 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 253 Per Group Analyzed (A vs. B vs. C vs. D): 64 vs. 68 vs. 60 vs. 61	A vs. B vs. C vs. D Age: NR Race: NR Sex (male): 81.4% (206/253), not reported by treatment group Smoking status: NR Recurrent bladder cancer: 37.5% (24/64) vs. 41.2% (28/68) vs. 43.3% (26/60) vs.45.9% (28/61) Stage: pTa: 10.9% (7/64) vs. 17.6% (12/68) vs. 6.7% (4/60) vs.9.8% (6/61); pT1: 89.1% (57/64) vs. 82.4% (56/68) vs. 93.3% (56/60) vs.90.2% (55/61); Tis associated: 6.3% (4/64) vs. 11.8% (8/68) vs. 0.0% (0/60) vs.0.0% (0/61) Grade: G1: 9.4% (6/64) vs. 16.2% (11/68) vs. 16.7% (10/60) vs.19.7% (12/61); G2: 78.1% (50/64) vs. 69.1% (47/68) vs. 70.0% (42/60) vs.65.6% (40/61); G3: 12.5% (8/64) vs. 14.7% (10/68) vs. 13.3% (8/60) vs.14.7% (9/61) Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	A vs. B vs. C vs. D Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61), A, B, and C vs. D, p = 0.0002, A and B vs. C, p = 0.02, A vs. B, p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4); A, B, and C vs. D, p < 0.001; B vs. C, p = 0.05; A and B vs. C; p = 0.05. Recurrence rate per 100 patient-months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p < 0.001, A and B vs. C; p < 0.05, A vs. B, p < 0.05. Progression (to muscle invasive): 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), p = 0.6.	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 0.0% (0/16) vs. 0.0% (0/12) vs. 0.0% (0/22) vs. 2.5% (1/40), p > 0.05; T1: 93.8% (15/16) vs. 83.3% (10/12) vs. 100% (22/22) vs. 97.5% (39/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p = 0.01, A vs. B, p = NS; pTis: 6.3% (1/16) vs. 16.7% (2/12) vs. NA vs. NA. Simple recurrence rate according to grade: G1: 0.0% (0/16) vs. 16.7% (2/12) vs. 13.6% (3/22) vs. 12.5% (5/40), p > 0.05; G2: 75.0% (12/16) vs. 58.3% (7/12) vs. 68.2% (15/22) vs. 67.5% (27/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p = 0.04, A vs. B, p = NS; G3: 25.0% (4/16) vs. 25.0% (3/12) vs. 18.2% (4/22) vs. 20.0% (8/40), p > 0.05. Simple recurrence rate according to Grade 3-Stage pT1/Total: 66.7% (4/6) vs. 37.5% (3/8) vs. 57.1% (4/7) vs. 100% (8/8); A, B, and C vs. D, p < 0.05; A and B vs. C, p > 0.05.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	A vs. B Simple recurrence rate: 25.0% (16/64) vs. 17.6% (12/68), p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4). Recurrence rate per 100 patient-months: 0.83 vs. 0.60, p < 0.05. Progression: 10.9% (7/64) vs. 4.4% (3/68) Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44)	NR	A vs. B vs. C (No data for group D) Proportion of patients with an adverse event: 15.6% (10/64) vs. 23.5% (16/68) vs. 41.7% (25/60), A and B vs. C, p = 0.002, A vs. B, p = 0.3, B vs. C, p < 0.04. Adverse events per # of installations: 7.3% (88/1199) vs. 8.7% (111/1280) vs. 29.0% (324/1118), A and B vs. C, p < 0.0001, B vs. C, p < 0.05. Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) vs. 12.0% (3/25), p < 0.05 Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) vs. 60.0% (15/25), A and B vs. C, p = 0.02, A vs. B, p > 0.05, B vs. C, p = 0.3. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) vs. 12.0% (3/25), A and B vs. C, p > 0.05, A vs. B, p > 0.05, B vs. C, p > 0.05. Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) vs. 8.0% (2/25) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) vs. 4.0% (1/25) UTI: 10.0% (1/10) vs. 0.0% (0/16) vs. 4.0% (1/25)	NR	Note: Possible overlap of some study subjects (group A) with those in Ali-El-Dein, 1997 (British J Urol)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1999[53] RCT High	Egypt Single center 1993-1997	Grade 2 or 3, stage pT1 disease, rapid disease recurrence within 6 months of initial resection, multicentricity, aneuploid DNA pattern, tumor size equal to or not more than 3 cm, assoc carcinoma in situ or other dysplastic mucosal changes and/or positive postoperative urinary cytology	Prior pelvic radiotherapy or systemic chenotherapy	1-3 weeks after transurethral resection of bladder tumor: A. BCG/epirubicin: alternating weekly 150 mg Pasteur strain 5x10^8 to 5x1069 CFU BCG with 50 mg epirubicin in 50 ml saline for 2 hours B. BCG only: 150 mg in 50 ml saline for 2 hours Treatment was weekly for 6 weeks then monthly for 10 months
Bilen, 2000[95] RCT Medium	Turkey Single-center 1994-1995	Superficial transitional-cell carcinoma of the bladder; patients with pT1 who had an additional one of four prognostic factors (grade 3 tumors, multiple tumors, tumors greater than 40 mm, recurrent tumors) were included	Patients with Ta tumors, previous treatment with any kind of intravesical therapy, radiotherapy, systemic chemotherapy were excluded	A. BCG 81 mg (Connaught strain) weekly for 6 weeks B. Sequential BCG 81 mg (Connaught) and epirubicin 50 mg with epirubicin given weeks 1, 2, 3, 4, and 12 and BCG given weeks 5, 6, 7, 9, 10, and 11

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1999[53] RCT High	Patients evaluated every 3 months for 2 years then every 6 months thereafter with: cystourethroscopy, urine cytology and flow cytometry mean followup: 30 months	Screened: Not reported Randomized: 139 Post-randomization exclusions: 15 (11%) due to severe side effects (3 vs 12) Loss to followup: not reported Analyzed: 124 (66 vs 58)	Age (mean): 57 vs 59 Male: 81% vs 72% Race: Not reported Smoking: Not reported Stage: Ta: 8% vs 7% T1: 92% vs 93% CIS: 11% vs 2% Grade: Grade 1: 12% vs 10% Grade 2: 55% vs 57% Grade 3: 33% vs 33%
Bilen, 2000[95] RCT Medium	3-monthly cystoscopies for first year and biannually thereafter median followup: 18 months	Screened: Not reported Randomized: 41 (21 vs 20) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 41 (21 vs 20)	Age (mean): 53 vs 57 Male: 95% vs 95% Race: Not reported Smoking: Not reported Grade: Grade 1: 3 (14%) vs 2 (10%) Grade 2: 14 (67%) vs 13 (65%) Grade 3: 4 (19%) vs 5 (25%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1999[53] RCT High	Recurrence: 11% (7/66) vs 21% (12/58) Progression: 5% (3/66) vs 9% (5/58)	
Bilen, 2000[95] RCT Medium	Recurrence: 4 (19%) vs 3 (15%) Progression: 2 (10%) vs 1 (5%) Median time to first recurrence: 16 months vs 11 months, p>0.05	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1999[53] RCT High			Withdrawals due to AE: 15 post-randomization exclusions due to severe side effects Overall toxicity: 27% vs 71% (p=0.001) Systemic toxicity: 6% vs 36% (p=0.001) Cystitis: 27% vs 62% Hematuria: 0% vs 7% Postponed treatment: 6% vs 17% (p=0.03) Discontinued treatment 4% vs 17% (p=0.02)	NR	
Bilen, 2000[95] RCT Medium			Irritative bladder symptoms: 9 (43%) vs 7 (35%) Hematuria: 8 (38%) vs 4 (20%) Fever: 3 (14%) vs 2 (10%) Contracted bladder 0 vs 1 (5%)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Boccardo, 1994[96] RCT Medium	Italy Number sites: Unclear (authors from 5 centers) Study years (enrollment): March 1987 - December 1989	Primary superficial bladder cancer (no prior history of bladder tumors). Stages and Grade: pTa G2; pT1 G1; pT1 G2. Negative urine cytology after TURBT; No previous local or systemic treatment for the disease; No evidence of concurrent conditions that might alter compliance with protocol; geographic ineligibility.	Primary or secondary CIS; Tumors involving prostatic urethra; urethral stenosis; active urinary infection.	A: Mitomycin (MMC), 40 mg (in 50 mL saline) intravesical, with retention "suggested" for 120 minutes; weekly dose X 8 weeks. Drug retained in bladder for approx. 120 minutes: yes, 124 (87.9%); no, 10 (7.1%); unknown, 7 (5.0%). B: Interferon alfa-2b (IFN), 50 X 106 IU (in 50 mL saline) intravesical, with retention "suggested" for 120 minutes; weekly dose X 8 weeks. Drug retained in bladder for approx. 120 minutes: yes, 135 (92.4%); no, 8 (5.5%); unknown, 3 (2.1%).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Boccardo, 1994[96] RCT Medium	42 months, maximum; Not reported as median/mean, nor for each group. Cystoscopy: 1 mo. after treatment; then every 3 mos. during first year; every 4 mos. during second year; then every 6 mos. Urine cytology on 3 samples before each cystoscopy; if persistent positive cytology with negative cystoscopy, bladder mapping performed.	Screened: NR Randomized: 287 Postrandomization exclusions: none Lost to followup: none Total Analyzed: 287 Per Group Analyzed: A: 141; B: 146	A vs. B Age, median (range): 64 yrs (33 - 82) vs. 63 yrs (20 - 79). Sex (male): 87.9% (124/141) vs. 84.9% (124/146) Race: Not reported Smoking status: NR Recurrent bladder cancer: None Stage/Grade: pTa/G2: 55.3% (78/141) vs. 53.4% (78/146), pT1/G1-G2: 45.7% (63/141) vs. 45.6%(68/146) Functional Status: NR Size: < 3 cm: 75.2% (106/141) vs. 78.1% (114/146); ≥ 3 cm: 24.1% (34/141) vs. 21.9% (32/146) Number of tumors: 1: 63.2% (89/141) vs. 61.7% (90/146); 2: 14.9% (21/141) vs. 17.1% (25/146); 3+: 20.5% (29/141) vs. 21.2% (31/146)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Boccardo, 1994[96] RCT Medium	A vs. B Patients with recurrence, % (n/N): 36.9% (52/141) vs. 47.9% (70/146) Relative recurrence rate: 0.82 vs. 1.2; p = 0.04 Recurrence risk ratio: 0.68 Median time to recurrence (months): 36.0 vs. 21.0; p = 0.048 Recurrence rate/100 patient/month: 2.4 vs. 3.4; p =0.04 Patients developing muscle-invasive cancer or advance in stage: 5.7% (8/141) vs. 3.4% (5/146)	Median time to recurrence (months): A vs. B: Stage pTa: "Not reached" vs. 20.0; p = 0.004 Stage pT1: 19.0 vs. 27.0; p = 0.84 Grade G1: Median times not reported; p = 0.43 Grade G2: 36.0 vs. 20.0; p = 0.014 Relative risk of recurring (RR (95% CI)), A; B: Stage (pT1 vs. pTa (ref)): 2.41 (1.21-4.77), p = 0.013; 0.93 (0.55-1.58), p = 0.81 Grade (G2 vs. G1(ref)):1.73 (0.81-3.7), p = 0.15; 2.3 (1.01-5.2), p = 0.035 Tumor size (≥ 3cm vs. < 3 cm (ref)): 1.03 (0.52-2.00), p = 0.93; 1.26 (0.71-2.21), p = 0.43 Number of tumors (multiple vs. single (ref)): 1.49 (0.85-2.6), p = 0.16; 2.4 (1.47-3.86), p < 0.001

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Boccardo, 1994[96] RCT Medium	NR	Relative risk of recurring (RR (95% CI)) A; B: Age (> 60 yrs vs. ≤ 60 yrs(ref)): 1.12 (0.61-2.05), p = 0.70; 1.01 (0.62-1.68), p = 0.93 Sex (female vs. male(ref)): 1.42 (0.58-3.45), p = 0.45; 1.02 (0.53-1.94), p = 0.96	Withdrawals due to AE: none reported A vs. B (%) Local: Dysuria: 46.3 vs. 42.7; p = NS Pollakiuria: 47.0 vs. 40.6; p = NS Strangury: 45.5 vs. 30.8; p = 0.01 Hematuria: 19.4 vs. 9.8; p = 0.02 Systemic: Hematologic: 0.7 vs. 2.5; p = NS Gastrointestinal: 1.7 vs. 2.4; p = NS Muscular: 1.5 vs. 0.7; p = NS Neurologic: 1.7 vs. 3.1; p = NS Fever: 1.4 vs. 11.2; p = 0.003	Schering-Plough, Milan, Italy (in part)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Cai, 2008[97] RCT Medium	Italy Single center 2005-2007	High risk NMIBC patients with recurrent urothelial cancer and with tumor recurrence at same stage and grade of the initial tumor at diagnosis	Locally infiltrative or metastatic tumors (T2 or greater), upper urinary tract tumors, lesions which could not be completely removed transurethrally, other neoplastic diseases, lower urinary tract diseases or major concomitant disease	After TURBT: A. Epirubicin/BCG: 80 mg Epirubicin in 50 ml normal saline within 6 hours of surgery; weekly x 6 instillations with 5 x 10^8 CFU OncoTICE BCG in 50 ml saline with boosters of BCG given at 3, 6, 12, 18, 24, 30, and 36 months B. BCG: weekly x 6 instillations with 5 x 10^8 CFU OncoTICE BCG in 50 ml saline with boosters of BCG given at 3, 6, 12, 18, 24, 30, and 36 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Cai, 2008[97] RCT Medium	Urine cytology, ultrasound and cystoscopy with biopsies of suspicious lesions every 3 months; selected patients with previous CIS also underwent multiple bladder cold cup biopsies at first cystoscopy Median Followup: 15 months vs 15 months	Screened: Not reported Randomized: 163 Post-randomization exclusions: none reported Loss to followup: 2 who were then excluded from the study Analyzed: 161 (80 vs 81)	Age (mean): 74 vs 70 Male: 85% vs 86% Race: Not reported Smoking: Not reported Stage: Ta: 74% vs 78% T1: 26% vs 22% Grade: Grade 2: 39% vs 33% Grade 3: 61% vs 67% CIS: 20% vs 22%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Cai, 2008[97] RCT Medium	Recurrence: 43% (34/80) vs 49% (40/81), p=0.82 Progression to invasive disease: 3% (2/80) vs 5% (4/81), p=0.32 No evidence of disease at followup: 58% (46/80) vs 51% (41/81), p=0.82	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cai, 2008[97] RCT Medium			Withdrawals due to AE: Not reported Painful urination: 3% (2/80) vs 1% (1/81)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Cheng, 2005[56] RCT Medium	China Single-center 1991-1999	Superficial bladder cancer (Ta or T1) with one or more of the following: stage>a, grade>1size>1cm or multiple or recurrent tumors	Carcinoma in situ or previous intravesical treatment	A. BCG 81 mg (Connaught strain) 6 weeks, maintenance course 10 months B. Epirubicin 50mg weekly for 4 weeks, monthly for 5 months and then 3 monthly for 6 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Cheng, 2005[56] RCT Medium	Cystoscopy every 3 months for 2 years, urine cytology every 6 months Median followup: 23 months (range 0-125 months) for recurrence, 47 months (0-127 months) for progression, 61 months (3-127 months) for survival	Screened: Not reported Randomized: 209 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 209 (102 vs 107)	Age (mean): 70 vs 70 Male: 72% vs 71% Race: Not reported Smoking: Not reported Stage: Ta: 63 (62%) vs 77 (72%) T1: 39 (38%) vs 29 (27%) Grade: Grade 1: 19 (19%) vs 30 (28%) Grade 2: 47 (46%) vs 55 (51%) Grade 3: 33 (32%) vs 20 (19%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Cheng, 2005[56] RCT Medium	Patients with recurrences: 30 (29%) vs 59 (55%) Median time to first recurrence 7 months vs 8 months Progression 16 (16%) vs 16 (15%) Median time to progression: 17.5 months vs 22 months Died of bladder cancer: 13 (13%) vs 7 (7%) Overall mortality: 41 (40%) vs 41 (38%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cheng, 2005[56] RCT Medium			NR	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Cho, 2009[98] RCT Medium	Korea Single Center 2005-2006	Patients with intermediate-risk (i.e., Ta, T1, G1-G2 multifocal, recurrent lesions > 3 cm, or high-risk (T1, G3 lesions or CIS) were included	Low risk (i.e., single Ta, G1 lesion < 3 cm)	A. BCG 12.5 mg 6 weekly instillations B. GEM 1000 mg perioperatively then 2000 mg at week 1, then BCG weekly for 6 weeks

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Cho, 2009[98] RCT Medium	Cystoscopy and cytology every 3 months Mean followup 32 and 34 months	Screened: Not reported Randomized: 87 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 87 (51 vs 36)	Age: 63 vs 64 Male: 94% vs 89% Race: Not reported Smoking: Not reported Stage: Ta: 18 (35%) vs 14 (39%) T1: 33 (65%) vs 22 (61%) CIS: 7 (14%) vs 5 (14%) Grade: Grade 1: 2 (4%) vs 2 (6%) Grade 2: 26 (51%) vs 21 (58%) Grade 3: 23 (45%) vs 13 (36%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Cho, 2009[98] RCT Medium	Patients with recurrences: 17 (33%) vs 14 (39%) Progression: 5 (10%) vs 3 (8%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cho, 2009[98] RCT Medium			Dysuria: 17 (33%) vs 13 (36%) Hematuria: 3 (6%) vs 7 (19%)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
De Reijke, 2005[99] RCT Medium	Europe Multi-center 1993-1999	Patients with biopsy proven primary, secondary or concurrent carcinoma in-situ (CIS) of the bladder with or without primary urinary cytology.	CIS in the prostrate stroma, previous pelvic irradiation, concurrent or previous muscle invasive disease	A. Epirubicin 50mg intravesical 8 weekly instillations followed by maintenance instillations at months 3, 6, 12, 18, 24, 30, 36 B. BCG 81 mg (Connaught strain) 6 weekly installations, followed by maintenance instillations at months 3, 6, 12, 18, 24, 30, 36

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
De Reijke, 2005[99] RCT Medium	Cystoscopy at 10 weeks, 6 months and every 3 months thereafter for 2 years and every 6 months thereafter if patient remained in complete response Median followup: 67 months	Screened: Not reported Randomized:168 (84 vs 84) Post-randomization exclusions: 7 (ineligible: 4 vs 3) Loss to followup: None reported Analyzed: 169 (84 vs 84)	Age: <60 years 19 (23%) 22 (26%) 60-69 years: 28 (33%) vs 27 (32%) 70-79 years: 32 (38%) vs 30 (36%) 80 or older: 4 (5%) vs 4 (5%) Male: 89% vs 94% Race: Not reported Smoking: Not reported Primary CIS: 19 (23%) vs 20 (24%) Secondary CIS: 22 (26%) vs 19 (23%) Concurrent CIS: 43 (51%) vs 44 (52%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
De Reijke, 2005[99] RCT Medium	Complete response: 47 (56%) vs 55 (65%), p=0.21 Complete response for primary CIS: 63% vs 60% Complete response for secondary CIS: 59% vs 63% Complete response for concurrent CIS: 51% vs 69% Progression: 4 (5%) vs 4 (5%) Time to first recurrence (median): 1.4 years vs 5.1 years, p=0.0004 Progression: 23 (27%) vs 15 (18%) Mortality: 34 (40%) vs 26 (31%) Died due to bladder cancer: 13 (15%) vs 9 (11%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
De Reijke, 2005[99] RCT Medium			Withdrawals due to AE 8 (10%) vs 26 (31%) Hematuria: 23 (28%) vs 33 (41%) Severe dysuria: 8 (10%) vs 19 (24%) Chemical cystitis: 2 (2%) vs 14 (18%) Local symptoms: 5 (6%) vs. 6 (20%)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
DeBruyne, 1992[100] RCT Medium DeBruyne, 1988[101] RCT Medium Witjes, 1998[102] RCT Medium	The Netherlands, the UK, Belgium Multicenter 1985-1986	Primary or recurrent superficial bladder cancer, including CIS, Ta, T1	Patients treated previously with intravesical or systemic cytotoxic agents or with radiotherapy	A. MMC 30 mg in 50 ml saline weekly for 4 weeks then monthly for 6 months B. BCG-RIVM (5 x 10^8 CFU) in 50 ml saline weekly for 6 weeks

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
DeBruyne, 1992[100] RCT Medium DeBruyne, 1988[101] RCT Medium Witjes, 1998[102] RCT Medium	Cystoscopies every 3 months Median followup: 21 months	Screened: Not reported Randomized: 361 Post-randomization exclusions: 17 Loss to followup: 9 (3 vs 6) Analyzed: 325 (167 vs 158)	Age <50: 20 (12%) vs 8 (14%) Age 50-59: 25 (14%) vs 36 (21%) Age 60-69: 63 (36%) vs 54 (32%) Age 70-79: 48 (28%) vs 57(33%) Age >79: 17 (10%) vs 10 (8%) Male: 80% vs 83% Race: Not reported Smoking: Not reported Stage: pTa: 110 (64%) vs 107 (63%) pT1: 58 (33%) vs 59 (34%) pTis only: 5 (3%) vs 5 (3%) CIS: 16 (9%) vs 24 (14%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
DeBruyne, 1992[100] RCT Medium DeBruyne, 1988[101] RCT Medium Witjes, 1998[102] RCT Medium	Recurrence: 60 (36%) vs 66 (42%) <u>7 year followup</u>: Recurrence 72 (43%) vs 76 (48%) Progression 12 (7%) vs 21 (12%) Mortality: 51 vs 46 Malignant disease: 18 vs 15	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
DeBruyne, 1992[100] RCT Medium DeBruyne, 1988[101] RCT Medium Witjes, 1998[102] RCT Medium			Drug-induced cystitis: 37 (21%) vs 30 (18%) Stopped treatment due to AE: 5 (3%) vs 3 (2%)	National Cancer Institute	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Di Lorenzo, 2010[103] RCT Low	Italy Multi-center 2006-2008	Patients with high risk NMIBC based on the European Organization for Research and Treatment of Cancer Scoring System failing BCG therapy for whom radical cystectomy was indicated but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiological risk.	Concurrent or previous MIBC or tumor in the upper urinary tract or prostatic urethra, chronic urinary tract infection, previous pelvic irradiation	A. Gemcitabine twice weekly (Day 1 and 4) at a dose of 2000mg/50mL for 6 consecutive weeks, and then weekly for 3 consecutive weeks at 3, 6 and 12 months B. BCG 81mg/50 ml (Connaught strain) over 6 weeks and then each week for 3 weeks at 3, 6 and 12 months
Di Stasi, 2003[104] Prospective Randomized Study Low	Italy Not reported 1994-2001	Adequate bone marrow reserve; normal renal function; normal liver function; a Karonofsky performance score of 50 to 100; reliable for long-term followup	Prior carcinoma of the bladder and/or upper urinary tract; other malignancies within 5 years of registration; pregnancy	A. BCG 81 mg wet weight (Pasteur) lyophilized and suspended in 50 mL bacteriostatic-free NaCl 0.9% solution retained for 120 minutes B. Passive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, held for 60 minutes C. Electromotive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, with 20 mA pulsed electronic current for 30 minutes All groups received 6 weekly treatments, with 10 monthly treatments for patients with a complete response and 6 more weekly treatments for those with persisting disease. A crossover in treatment for those with persisting disease after 6 months.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Di Lorenzo, 2010[103] RCT Low	Median followup 15 months	Screened: 92 Randomized: 40 vs 40 Post-randomization exclusion: None reported Loss to followup: None reported Analyzed: 80 (40 vs 40)	Age (mean): 69 vs 71 Male: 68% vs 55% Race: Not reported Smoking: Not reported Stage: Ta: 10 (25%) vs 8 (20%) T1: 30 (75%) vs 32 (80%) Grade: Grade low: 11 (28%) vs 13 (33%) Grade high: 29 (73%) vs 27 (68%)
Di Stasi, 2003[104] Prospective Randomized Study Low	Cystoscopy, biopsy and urinary cytology. Biopsies at 3 and 6 months, thereafter only if indicated by suspicious cytological findings or cystoscopy. In tumor-free cases cystoscopy and urinary cytology were repeated at 3 month intervals fir 2 years, 6 month intervals for 3 years and yearly thereafter Median followup: 43 vs 42 vs 45 months	Screened: 117 Randomized: 108 (36 vs 36 vs 36) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 108 (36 vs 36 vs 36)	Age (median): 66.5 vs 68.5 vs 64.5 Male: 75% vs 72% vs 72% Race: Not reported Smoking: Not reported Stage: Cis only: 3 (8.3%) vs 3 (8.3%) vs 4 (11.1%) Cis + pTa: 33 (91.7%) vs 33 (91.7%) vs 32 (88.9%) Grade: Grade 2: 19 (57.6%) vs 19 (57.6%) vs 18 (56.3%) Grade 3: 14 (42.4%) vs 14 (42.4%) vs 14 (43.7%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Di Lorenzo, 2010[103] RCT Low	Patients with recurrences: 21 (53%) vs 35 (88%), p=0.002 Time to first recurrence: 3.9 months vs 3.1 months; p=0.9 2 yr recurrence-free survival: 19% vs 3%, p<0.008 Progression: 7 (33%) vs 13 (38%) Deaths: 0 vs 1	
Di Stasi, 2003[104] Prospective Randomized Study Low	Recurrence: 52.8% vs 75% vs 52.8% Progression: 16.7% vs 22.2% vs 16.7% Mortality: 11/36 vs 12/36 vs 9/36	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Di Lorenzo, 2010[103] RCT Low			Dysuria: 6 (15%) vs 8 (20%) Hematuria: 2 (5%) vs 5 (13%) Fever: 1 (3%) vs 3 (8%)	NR	
Di Stasi, 2003[104] Prospective Randomized Study Low			Withdrawals due to adverse events: 4 (11.1%) vs 5 (5.6%) vs 3 (8.3%) Drug induced cystitis: 24 (66.7%) vs 9 (25.0%) vs 13 (36.1%) Visible hematuria: 26 (72.2%) vs 6 (16.7%) vs 8 (22.2%) Fever: 7 (19.4%) vs 0 vs 0	Progetti di Ricerca di Ateneo; Tor Vergata University of Rome; Physion Srl, Medolla, Italy.	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Duckek, 2010[105] RCT Low Hemdan, 2014[106]	Sweden, Norway, Finland Multicenter 1999-2006	Patients with newly detected T1 G2-G3 urinary bladder cancer.	Recurrent bladder tumor of any stage, MIBC at a second look resection, involvement of the urethra, prostate or upper urinary tract, a history of radiotherapy or systemic chemotherapy, previous endovesical treatment, with the investigational drugs other than a single instillation of chemotherapy including epirubicin after TURB	A. BCG 2ml in 100ml saline (OncoTICE) B. Epirubicin 50mg dry substance+10 million units of IFN-2b (dissolved in 100 ml saline) Both regimens induction treatment: 6 weeks, maintenance treatment 2 years
Ersoy, 2013[58] RCT High	Turkey Single site Study years: February 2006 - November 2010	Primary low-risk non-muscle-invasive bladder cancer (NMIBC). Stage Ta, Grade G1. Solitary tumor; Size < 3 cm.	"Medium or high risk NMIBC"; Muscle-invasive bladder cancer; Suspected bladder perforation.	A: Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Duckek, 2010[105] RCT Low Hemdan, 2014[106]	Cystoscopy and cytology every 3 months for the first 2 years, and every 6 months thereafter until 5 years from start of treatment Followup: 24 months Median followup: 6.9 years	Screened: Not reported Randomized: 256 (128 vs 128) Post randomization exclusions: 2 vs 4 Loss to followup: None reported Analyzed: 250 (126 vs 124)	Age (mean): 66 vs 67 Male: 80% vs 78% Race: Not reported Smoking status: Not reported Grade: Grade 2: 35 (28%) vs 32 (26%) Grade 3: 91 (72%) vs 92 (74%)
Ersoy, 2013[58] RCT High	A vs. B vs, C Median (range): 51 months (12-60) vs. 50 months (12-59) vs. 54 months (38-60), p = 0.815 Cystoscopy: month 3, month 12, then annually for 5 years. Patients with macroscopic or microscopic hematuria underwent ultrasound and cystoscopy. Urinary pH (groups A and B only): measured night before TURBT and just prior to TURBT.	Screened: NR Randomized: 53 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 49 Per Group Analyzed (A vs. B vs. C): 11 vs. 15 vs. 23	A vs. B vs. C Age, mean (± SD): 59.3 yrs (± 14.9) vs. 63.5 yrs (± 15.0) vs. 61.9 yrs (± 10.2), p = 0.716 Race: NR Sex (male): 81.8% (9/11) vs. 86.7% (13/15) vs. 95.7% (22/23), p = 0.395 "History of smoking": "None": 36.4% vs. 26.7% vs. 8.7%; "Present": 63.6% vs. 73.3% vs. 91.3%; p = 0.124 (for "History of Smoking") Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 100% vs. 100% Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Duckek, 2010[105] RCT Low Hemdan, 2014[106]	Recurrence or progression at 6 months: 34 (27%) vs 47 (38%), p=0.065 Disease-free survival: favors BCG, p=0.012 Progression-free survival: no difference between groups	
Ersoy, 2013[58] RCT High	A vs. B vs. C Recurrence free at 1 year: 100% vs. 86.7% vs. 91.3%; A vs. B, p = 0.132; A vs. C, p = 0.173 Recurrence free at 3 years: 100% vs. 79.4% vs. 82.6%; A vs. B, p = 0.132; B vs. C, p = 0.645 Recurrence free at 5 years: 100% vs. 79.4% vs. 82.6%; A vs. C, p = 0.173; B vs. C, p = 0.645 Mean time to recurrence, months (95% CI): NA vs. 34.8 (28.5-41.1) vs. 51.8 (47.7-57.7)	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Duckek, 2010[105] RCT Low Hemdan, 2014[106]			Withdrawals due to adverse events: 11 (8%) vs 2 (2%), p=0.06	Cancerforkningsfonden, Pharmacia and Upjohn, Schering-Plough Nordic Biotech, and Organon Teknika AB	
Ersoy, 2013[58] RCT High	NR	A vs. B vs. C Recurrence free survival according to sex, (p = 0.769): Male, 1-year: 90.9%; 3-years: 85.9%; 5-years: 85.9% Female, 1-year: 100.0%; 3-years: 66.7%; 5-years: NR Mean time to recurrence according to sex, months (95% CI): Male: 53.0 (47.7-58.2) Female: 44.9 (28.6-61.1) Recurrence free survival according to history of	NR	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Eto, 1994[107] RCT Medium	Japan Number sites: 21 Study years: January 1990 - December 1992	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	Presence of another cancer, residual tumor, CIS; previous treatment with doxorubicin or derivatives; severe dysfunction of heart, liver, kidney or bone marrow; severe complications; poor general condition suggesting that survival for duration of study was unlikely.	A: Epirubicin, 30 mg (in 30 mL physiological saline). B: Doxorubicin, 30 mg (in 30 mL physiological saline). Each group received 19 intravesical installations over 1 year. Installations performed 2 times/week for 4 weeks, then 1 time/month for 11 months.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Eto, 1994[107] RCT Medium	A vs. B Mean (± SD): 674 days (± 315) vs. 606 (± 318) Cystoscopy every 3 months for 3 years. Urinary cytology monthly for 1 year, then every 3 months for 3 years.	Screened: NR Randomized: 150 Postrandomization exclusions: 22 ("data not collected" = 20; protocol violation = 2) (not reported by group) Other excluded (not eligible): 6 (not reported by group) Lost to followup: 8 (not reported by group) Total Analyzed: 114 Per Group Analyzed (A vs. B): 60 vs. 54	A vs. B Age, median (range): 65 yrs (24 - 89) vs. 67 yrs (39 - 87); p < 0.01 Race: NR Sex (male): 85.0% (51/60) vs. 87.0% (47/54) Smoking status: NR Recurrent bladder cancer: 14.8% (8/54) vs. 16.3% (8/49); Unknown: 10% (6/60) vs. 9.3% (5/54); p = NS Stage: Ta: 35.0% (21/60) vs. 31.5% (17/54); T1: 48.3% (29/60) vs. 57.4% (31/54); Unknown: 16.7% (10/60) vs. 11.1% (6/54); p = NS Grade: G1: 33.3% (20/60) vs. 20.4% (11/54); G2: 48.3% (29/60) vs. 66.7% (36/54); G3: 11.7% (7/60) vs. 7.4% (4/54); Unknown: 6.7% (4/60) vs. 5.6% (3/54): p = NS Functional Status: NR Size: < 1 cm: 45% (27/60) vs. 50% (27/54); 1- 3 cm: 40% (24/60) vs. 46% (25/54); 3-5 cm: 13% (8/60) vs. 4% (2/54); > 5 cm: 17% (1/60) vs. 0% (0/54) Number of tumors: 1: 47% (28/60) vs. 63% (34/54); 2-4: 38% (23/60) vs. 22% (12/54); ≥ 5: 12% (7/60) vs. 11% (6/54)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Eto, 1994[107] RCT Medium	A vs. B Recurrence (at 1 year): 6.7% (4/60) vs. 13.0% (7/54) Recurrence free at 1 year, generalized Wilcoxon test, p = non-significant. Recurrence (at 2 years): 11.6% (7/60) vs. 18.5% (10/54) Recurrence free at 2 years, generalized Wilcoxon test, p = non-significant.	A vs. B Recurrence free at 1 year and 2 years according to: Stage Ta: 1 yr: 100.0% vs. 87.5%; 2 yrs: 100.0% vs. 87.5%; p = 0.201 Stage T1: 1 yr: 88.3% vs. 86.8%; 2 yrs: 83.6% vs. 82.9%; p = 0.554 Grade G1: 1 yr: 94.7% vs. 80.0%; 2 yrs: 94.7% vs. 80.0%; p = 0.509 Grade G2: 1 yr: 96.0% vs. 94.2%; 2 yrs: 96.0% vs. 87.5%; p = 0.225 Primary: 1 yr: 90.5% vs. 92.4%; 2 yrs: 87.6% vs. 86.6%; p = 0.966 Recurrent: 1 yr: 100.0% vs. 62.5%; 2 yrs: 87.5% vs. 62.5%; p = 0.091 Size < 1 cm: 1 yr: 100.0% vs. 91.8%; 2 yrs: 95.2% vs. 87.5%; p = 0.342 Size ≥1 cm:1 yr: 87.4% vs. 81.1%; 2 yrs: 83.6% vs.76.1%; p = 0.325 Single tumor: 1 yr: 92.4% vs. 85.1%; 2 yrs: 92.4% vs. 81.2%; p = 0.193 Multiple tumor: 1 yr: 92.9% vs. 88.5%; 2 yrs: 84.6% vs. 82.6%; p = 0.744

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Eto, 1994[107] RCT Medium	NR	NR	A vs. B Micturitional pain: 10.0% (6/60) vs. 14.8% (8/54); p = NS Pollakisuria: 15.0% (9/60) vs. 14.8% (8/54); p = NS Hematuria: 5.0% (3/60) vs. 0.0% (0/54)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Friedrich, 2007[108] RCT Medium	Germany, Multicenter 1995-2002	Patients with primary transitional cell carcinoma of the bladder or patients with tumor recurrence after TURBT without prior adjuvant therapy were eligible if the histopathologic evaluation of their completely resected tumor revealed an intermediate risk pTaG1 tumor (size>3cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with apT1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	MIBC or concomitant CIS, evidence of lymph node or distant metastasis, or a pT1G3 tumor≥2.5cm.	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations c. MMC 20 mg, 6 weekly instillations followed by monthly instillations of MMC 20mg for 3 years

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Friedrich, 2007[108] RCT Medium	Cytology and cystoscopy every 3 months in the first 2 years and every 6 months thereafter Median followup: 2.9 years	Screened: Not reported Randomized: 495 (179 vs 163 vs 153) Post randomization exclusions: None reported Loss to followup: 11% equally distributed between arms Analyzed: 495 (179 vs 163 vs 153)	Age (median): 68 vs 67 vs 67 Male: 79% vs 80% vs 82% Race: Not reported Smoking status: Not reported Stage/grade: TaG1: 15% vs 12% vs 5% TaG2: 54% vs 45% vs 54% TaG3: 2% vs 3% vs 2% T1G1: 3% vs 3% vs 2% T1G2: 22% vs 31% vs 27% T1G3: 3% vs 6% vs 11%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Friedrich, 2007[108] RCT Medium	Patients with recurrences:46 (26%) vs 41 (25%) vs 16 (10%) % recurrence-free at 2 years: 126 (71%) vs 112 (69%) vs 135 (88%) % recurrence-free at 3 years:123 (69%) vs 107 (66%) vs 132 (86%), difference between groups p=0.001. Pairwise comparison C superior to A (log-rank test, p=0.0006), or B (log-rank test , p=0.0005)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Friedrich, 2007[108] RCT Medium			Withdrawals due to AE: 0 vs 3 vs 8 Dysuria: 12% vs 17% vs 20% Hematuria: 1% vs 12% vs 9% Fever: 2% vs 9% vs 2%	Fa. Medac GmbH	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Giannakopoulos, S, 1998[2] RCT Medium	Greece Number sites: Unclear (authors from 3 centers) Study years: NR	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Stage ≥ T2. Grade G1 or G3 (any stage). CIS; Other concomitant malignancy; Serious systemic disease; Previous intravesical chemotherapy or immunotherapy; TCC of upper urinary tract; Previous systemic chemo/immunotherapy or pelvic radiation therapy	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (IFN-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (IFN-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (IFN-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First installation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Installations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.
Giannopoulos, A, 2003[109] RCT Medium	Greece Number sites: Multi-center. Number unclear (authors from 3 centers) Study years: January 1997 - February 2001	Superficial transitional cell carcinoma (TCC) of the bladder. Primary/ initial diagnosis. Stages Ta or T1; Grade G2. No more than 2 foci. Initial specimens sufficient to document absence of muscle invasion.	Previous history of cancer and immunodeficiency; Coexistence of CIS or high grade (G3) TCC; Suspicion of upper tract TCC.	A: Interferon-gamma 1b (IFN-γ 1b), 1.5 X 107 IU (or 0.5 mg), in 50 mL normal saline. Retained intravesically for 2.5 hours. Total 20 installations. First installation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. B: Mitomycin C, 40 mg (in 50 mL normal saline). Retained intravesically for 2.5 hours. Total 20 installations. First installation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Giannakopoulos, S, 1998[2] RCT Medium	36 months; Not reported as median/mean, nor for each group. Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter. Biopsy of previous scars and random bladder biopsies every 3 months for 18 months, and every 6 months thereafter. CBC and serum chemistry tests at every other installation.	Screened: NR Randomized: 89 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 89 Per Group Analyzed (A vs. B vs. C vs. D): 20 vs. 22 vs. 24 vs. 23	A vs. B vs. C vs. D Age, mean (SD): 61.6 yrs (9.62) vs. 62.1 yrs (9.49) vs. 60.9 yrs (9.43) vs. 61.9 yrs (9.98); p > 0.10 Race: NR Sex (male): 80.0% (16/20) vs. 81.8% (18/22) vs. 79.2% (19/24) vs. 82.6% (19/23); p > 0.10 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 60.0% (12/20) vs. 59.1% (13/22) vs. 62.5% (15/24) vs. 56.5% (13/23); T1: 40.0% (8/20) vs. 40.9% (9/22) vs. 37.5% (9/24) vs. 43.5% (10/23); p > 0.10 Grade: All G2 Functional Status: NR
Giannopoulos, A, 2003[109] RCT Medium	A vs. B Median (range): 26.5 months (4 - 45) vs. 24 months (3 - 49). Cystoscopy and urine cytology, every 3 months for 1 year, and every 6 months thereafter. Random cold cup biopsies from bladder wall urothelium during cystoscopy at 6 months and 12 months. Hematological, renal, and hepatic function testing every 3 months for 1 year, and every 6 months thereafter.	Screened: NR Randomized: 123 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 123 Per Group Analyzed (A vs. B): 60 vs. 63	A vs. B Age, median (range): 68 yrs (34 - 86) vs. 60 yrs (26 - 81); p < 0.966 Race: NR Sex (male): 80.0% (48/60) vs. 88.9% (56/63); p =0.27 Smoking status: NR Recurrent bladder cancer: None (all primary) Stage: Ta: 66.7% (40/60) vs. 60.3% (38/63); T1: 33.3% (20/60) vs. 39.7% (25/63) Grade: All G2 Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Giannakopoulos, S, 1998[2] RCT Medium	A vs. B vs. C vs. D Recurrence: 65.0% (13/20) vs. 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); A vs. B, p = 0.06; A vs. C, p < 0.05; A vs. D, p < 0.01; Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): 15.0 vs. 21.4 vs. 26.1 vs. 30.0; A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: 2.91 vs. 1.19 vs. 0.88 vs. 0.63; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: 30.0% (6/20) vs. 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); A vs. B, p = NS; A vs. C, p < 0.05; A vs. D, p < 0.05; B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS. Progression details: A: Ta to T1 (n = 3), T1 to MIBC (n = 3); B: Ta to T1 (n = 1), T1 to MIBC (n = 2); C: T1 to MIBC (n = 1); D: T1 to MIBC (n = 1).	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 53.8% (7/13) vs. 50.0% (4/8) vs. 57.1% (4/7) vs. 40.0% (2/5); For all comparisons between groups, p > 0.10. T1: 46.2% (6/13) vs. 50.0% (4/8) vs. 42.9% (3/7) vs. 60.0% (3/5); For all comparisons between groups, p > 0.10. Recurrence-free survival time according to stage, Mean months (SD): Ta: 15.4 (5.86) vs. 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); A vs. B, p < 0.01; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.05, B vs. D, p < 0.001; C vs. D, p = NS. T1: 14.5 (6.95) vs. 19.5 (9.33) vs. 23.0 (9.17) vs. 29.0 (7.55); A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p = 0.048, B vs. D, p < 0.001; C vs. D, p < 0.01. Recurrence rate per 100 patient-months according to stage: Ta: 2.43 vs. 0.96 vs. 0.78 vs. 0.44; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p < 0.001; Differences between B, C, and D, p = NS. T1: 3.77 vs. 1.55 vs. 1.05 vs. 0.8; Results "similar" to stage Ta, no p=values reported.
Giannopoulos, A, 2003[109] RCT Medium	A vs. B Recurrence-free at 1 year: 90.0% (54/60) vs. 76.2% (48/63) Recurrence-free for total study period: 73.3% (44/60) vs. 57.1% (36/63) Difference in recurrence-free survival time at 1 year, p = 0.04 Difference in recurrence-free survival time for total study period, p = 0.051	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Giannakopoulos, S, 1998[2] RCT Medium	B vs. C vs. D Simple recurrence rate: Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS.	NR	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups not reported) developed fevers and were found to have urinary tract infections.	NR	
Giannopoulos, A, 2003[109] RCT Medium	NR	NR	NR	Scientific Committee of the Central National Health Council of the Greek Ministry of Health; Scientific Committee of Special Account for Research of the National and Kapodistrian University of Athens	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gontero, 2013[110] RCT High	Italy, Germany, USA Multicenter 2006-2010	Intermediate risk NMIBC (namely Ta-1, G1-2, multifocal or unique and recurrent, more than 3 cm in diameter) were eligible if they met additional criteria of WHO performance status 2 or less, age 85 years or younger, BCG naïve, disease-free and not treated with intravesical chemotherapy in the last 3 months	Presence of T1G3 disease or CIS, preoperative urinary cytology positive for high grade atypia	A. BCG 27 mg (Connaught strain) in 50 ml saline, 6 weekly instillations, maintenance: 3 weekly instillations at 3, 6 and 12 months B. Gemcitabine 2000 mg in 500ml saline, 6 weekly instillations, maintenance consisted of monthly instillations up to 1 year

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gontero, 2013[110] RCT High	Cytology and cystoscopy every 3 months Followup: 1 year	Screened: Not reported Randomized: 120 (59 vs 61) Post randomization exclusions: 5 (2 vs 3) Lost to followup: None reported Analyzed: 88 (47 vs 41)	Age (mean) : 68 vs 67 Male: 85% vs 87% Race: Not reported Smoking: Not reported Stage: pta: 42 (71%) vs 42 (69%) pT1: 17 (29%) vs 19 (31%) Grade: Grade 1: 20 (34%) vs 17 (28%) Grade 2: 39 (66%) vs 44 (72%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gontero, 2013[110] RCT High	Patients with recurrence at 1 year: 14 (30%) vs 16 (39%), p=0.83 Mean recurrence free survival: 10.4 months vs 10.6 months, p=0.66 Progression: 3 (6%) vs 5 (12%), p=0.71 Mean progression free survival: 11.6 months vs 11.6 months, p=0.50	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gontero, 2013[110] RCT High			Local and systemic side effects: 40.4% vs 34.1% (p=0.66) Dysuria: p=0.01 (in favor of gemcitabine) Withdrawals due to AE: 1 vs 0 Dysuria: induction: 21 (36.8%) vs 13 (23.2%), p=0.15 1 yr: 15 (31.9%) vs 4 (9.7%), p=0.01 Hematuria: induction 9 (15.8%) vs 0 (0%), p=0.003 1 yr: 11 (23.4%) vs 4 (9.7%), p=0.15 Fever: induction10 (17.5%) vs 0 (0%), p=0.001 1 yr: 4 (8.5%) vs 2 (4.8%), p=0.68	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gulpinar, 2012[111] RCT Medium	Turkey Single-center 2004-2006	Patients with intermediate or high risk for recurrence and progression according to the EAU guidelines were included. Patients with stage pTaG1or pTaG2 tumors were included if tumor size>3cm or recurrent or multifocal tumors. Patients with CIS, pTaG3 tumors and all pT1 tumors were included, no instillations of chemotherapy or immunotherapy during the previous 6 months before entering the study	Muscle-invasive bladder tumor, evidence of lymph-node metastasis or distant metastasis, upper urinary tract tumors, tumors that could not be completely removed transurethral, presence of a second primary malignancy.	A. MMC 40mg in 40mL saline administered within 6 hours of surgery followed by delayed BCG instillations once a week for 6 weeks at least 15 days from TURBT B. Delayed BCG instillations (once a week for 6 weeks) at least 15 days from TURBT

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gulpinar, 2012[111] RCT Medium	Cystoscopy and cytology every third month for first 2 years and then every 6 months years 3 and 4 Median followup: 41 months vs 41 months	Screened: Not reported Randomized: 51 (25 vs 26) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 51 (25 vs 26)	Age mean): A: 58 vs 58 Male: 84% vs 77% Race: Not reported Smoking: Not reported Stage: T1: 44% vs 46% Grade: High Grade: 32% vs 23% CIS: 16% vs 19%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gulpinar, 2012[111] RCT Medium	Patients with recurrence: 9 (36%) vs 5 (19%),p=0.052 Median time to first recurrence: 8 months vs 7 months, p=0.012 Progression to muscle invasive disease: 1 vs 1 Recurrence-free survival: no difference between groups, p=0.959	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gulpinar, 2012[111] RCT Medium			Rates of AE: p=0.457 between groups Dysuria: A: 2 (8%) vs B: 3 (12%)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gustafson, 1991[60] RCT Medium	Sweden Number sites: Unclear. Authors from 4 centers Study years: NR	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	None explicitly stated. However, no patient had previously been treated with radiotherapy, systemic or topical chemotherapy.	A: Mitomycin C. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 ml" to "40 mg in 250 ml". First installation approximately 2 weeks after TURBT. Installations weekly X 4 weeks, then monthly X 11 months. B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 ml" to "80 mg in 250 ml". First installation approximately 2 weeks after TURBT. Installations weekly X 4 weeks, then monthly X 11 months. C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gustafson, 1991[60] RCT Medium	A vs. B vs. C Mean followup, months (range): 47 (12-65) vs. 45 (14-69) vs. 35 (10-68) Cystoscopy every 3 months during year 1; thereafter, every 6 months unless recurrence, in which case every 3 months. Micturition frequency, pain on micturition, other subjective symptoms recorded before and after each installation. Blood tests (including CBC and creatinine) after 2nd and 4th installation and every month, thereafter.	Screened: NR Randomized: 62 Postrandomization exclusions: NR Lost to followup: 2 Total Analyzed: 60 Per Group Analyzed: 19 vs. 20 vs. 21	A vs. B vs. C Age, mean (Overall; not reported by group): 67 years Race: NR Sex (Overall male: female; not reported by group): "Four to one" Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 89.5% (17/19) vs. 90.0% (18/20) vs. 95.2% (20/21); T1: 10.5% (2/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Grade: G1: 36.8% (7/19) vs. 35.0% (7/20) vs. 33.3% (7/21); G2: 63.2% (12/19) vs. 65.0% (13/20) vs. 61.9% (13/21); G3: 0% (0/19) vs. 0% (0/20) vs. 4.8% (1/21) Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gustafson, 1991[60] RCT Medium	A vs. B vs. C Recurrence: Tumor-free survival during treatment year: 52.6% (10/19) vs. 15% (3/20) vs. 14.3% (3/21) Tumor-free survival for duration of followup: 26.3% (5/19) vs. 10% (2/20) vs. 4.8% (1/21) Mean disease-free interval, months (A vs. B): 14 vs. 6, p = 0.02 Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p = 0.02 Progression: Increased stage: 0% (0/19) vs. 5% (1/20) vs. 4.8% (1/21) Increased grade: 0% (0/19) vs. 15% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10% (2/20) vs. 0% (0/21)	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gustafson, 1991[60] RCT Medium	NR	NR	No significant changes in frequency of micturition. No serious side-effects detected by blood samples. Mild pain on micturition (A vs. B): 60 % vs. 45%	King Gustaf V Jubilee Foundation	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hinosotu, 2011[112] RCT Medium	Japan Multicenter 2004-2006	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or © recurrence diagnosed within 12 months from previous TURBT for NMIBC	History of BCG instillation or an anthracycline anti-tumor drug within the 12 months following the day on which the TURBT was performed (1 course of BC more than 12 months earlier permitted and MMC therapy allowed after a washout period of at least 4 weeks); stage T2 or higher; IV/IA anticancer/ chemotherapy, radiation	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 ml saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 ml saline weekly for 6 weeks C. Epirubicin 40 mg in 40 ml saline twice at 1-week interval and then 7 times at 2-week intervals

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Hinosotu, 2011[112] RCT Medium	Cystoscopy and cytology every 3 months for 3 years then every 6 months Median followup: 2 years	Screened: Not reported Randomized: 116 Post-randomization exclusions: 5 in BCG maintenance group as had no maintenance instillations Loss to followup: None reported Analyzed: 110 (36 vs 42 vs 32)	Age ≤ 64: 17 vs 22 vs 11 Age > 64: 24 vs 20 vs 21 Male: 80% vs 95% vs 97% Race: Not reported Smoking: Not reported Stage: pTa: 29 (71%) vs 29 (69%) vs 24 (75%) pT1: 12 (29%) vs 13 (31%) vs 8 (26%) Grade: Grade 1: 5 (12%) vs 10 (24%) vs 4 (13%) Grade 2: 29 (71%) vs 24 (57%) vs 21 (68%) Grade 3: 7 (17%) vs 8 (19%) vs 7 (23%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Hinosotu, 2011[112] RCT Medium	Recurrence: 5 (12%) vs 14 (33%) vs 22 (69%) Progression at time of recurrence: 0 vs 3 (7%) vs 7 (22%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hinotsu, 2011[112] RCT Medium			Dysuria: 93% vs 69% vs NR Hematuria: 93% vs 71% vs NR Fever: 43% vs 26% vs NR	Nippon Kayaku Co. Ltd. (current Japanese license holder for the BCG Connaught strain)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hinotsu, 2006[113] RCT Medium	Japan 1998-2002	Histopathologically proven transitional cell carcinoma (Stage pTa or pT1 and grade 1 to 2)	Single primary lesion, previous BCG or doxorubicin instillations	A. BCG (Tokyo 172 strain) 80 mg in 40 ml saline-6 weekly instillations B. Doxorubicin 20 mg in 40 ml saline-17 instillations-twice performed once a week then once every other week seven times, then once a month eight times

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Hinotsu, 2006[113] RCT Medium	Cystoscopy every 3 months for 3 years and every 6 months thereafter Median followup: 667 days	Screened: Not reported Randomized: 83 (41 vs 42) Post-randomization exclusions: 3 found to be ineligible after registration (1 vs 2) Loss to followup: None reported Analyzed: 80 (40 vs 40)	Age (mean): 64 vs 63 Male: 80% vs 68% Race: Not reported Smoking: Not reported Stage: Ta: 19 (48%) vs 21 (53%) T1: 21 (53%) vs 19 (48%) Grade: Grade 1: 8 (20%) vs 8 (20%) Grade 2: 32 (80%) vs 30 (75%) Grade 3: 0 vs 2 (5%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Hinotsu, 2006[113] RCT Medium	Recurrence: favored BCG, p=0.02; "the hazard of recurrence in the BCG group was about one half of that in the doxorubicin group"	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hinotsu, 2006[113] RCT Medium			Dysuria: 28 vs 15, p=0.024 Hematuria: 21 vs 8, p=0.005 Fever: 13 vs 7, p=0.043	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Huland, 1990[114] RCT Medium	Germany (Hamburg) Number sites: 6 hospitals Study years: March 1983 - June 1985	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	"Prophylactic installation not possible because of patient age, immobility or lack of cooperation". Grade 0 tumor.	A: Mitomycin C, 20 mg/20 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: Mitomycin C, 20 mg/20 ml. Total 42 installations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: Mitomycin C, 20 mg/20 ml. Total 20 installations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Installations started 4 to 6 weeks after discharge from hospital.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Huland, 1990[114] RCT Medium	A vs. B vs. C vs. D Mean followup, months: 26.7 vs. 27.4 vs. 26.7 vs. 30.2 Patients followed by their own private urologists. Cystoscopy every 3 months. "Patients themselves performed the documentation". Patients "received from a central coordinator a form with data on the instillations and cytoscopic controls".	Screened: 597 Randomized: 477 Postrandomization exclusions: 29 Lost to followup: NR Total Analyzed: 419 Per Group Analyzed: 209 vs. 96 vs. 75 vs. 39	A vs. B vs. C vs. D Age, mean (men/women): 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs .68.0/58.3 Race: NR Sex (male): 82.3% (172/209) vs. 77.1% (74/96) vs. 77.3% (58/75) vs. 74.4% (29/39) Smoking status: NR Recurrent bladder cancer: 32.1% (67/209) vs. 25.0% (24/96) vs. 25.3% (19/75) vs. 43.6% (17/39) Stage: Ta: 73.7% (154/209) vs. 78.1% (75/96) vs. 76.0% (57/75) vs. 59.0% (23/39); T1: 23.0% (48/209) vs. 19.8% (19/96) vs. 21.3% (16/75) vs. 33.3% (13/39); Tis: 3.3% (7/209) vs. 2.1% (2/96) vs. 2.7% (2/75) vs. 7.7% (3/39) Grade: G1: 47.4% (99/209) vs. 58.3% (56/96) vs. 52.0% (39/75) vs. 43.6% (17/39); G2: 47.7% (99/209) vs. 35.4% (34/96) vs. 37.3% (28/75) vs. 38.5% (15/39); G3: 1.9% (4/209) vs. 4.2% (4/96) vs. 8.0% (6/75) vs. 10.3% (4/39) Functional Status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Huland, 1990[114] RCT Medium	A vs. B vs. C vs. D Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) vs. 23.1% (9/39) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 vs. 0.76 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) vs. 7.7% (3/39) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75) vs. 10.3% (4/39)	A vs. B vs. C vs. D Recurrence among patients with primary tumor (n = 288): By Stage: Ta: 9.6% (10/104) vs. 6% (3/50) vs. 15% (6/40) vs. 23.1% (3/13) T1: 14.7% (5/34) vs. 0% (0/17) vs. 13.3% (2/15) vs. 42.9% (3/7) CIS: 66.7% (2/3) vs. 0% (0/2) vs. 0% (0/1) vs. 0% (0/2) By Grade: G1: 7.9% (5/63) vs. 7.5% (3/40) vs. 14.3& (4/28) vs. 0% (0/9) G2: 12.7% (9/71) vs. 0% (0/24) vs. 13.0% (3/23) vs. 50% (4/8) G3: 9% (1/9) vs. 0% (0/3) vs. 0% (0/5) vs. 20% (1/5) Recurrence among patients with recurrent tumor in the past (n = 131): By Stage: Ta: 28.0% (14/50) vs. 20% (5/25) vs. 29.4% (5/17) vs. 10% (1/10) T1: 7.1% (1/14) vs. 50% (1/2) vs. 0% (0/1) vs. 16.7% (1/6) CIS: 0% (0/4) vs. 0% (0/0) vs. 0% (0/1) vs. 100% (1/1) By Grade: G1: 13.9% (5/36) vs. 25% (4/16) vs 9.1% (1/11) vs. 0% (0/8) G2: 35.7% (10/28) vs. 20% (2/10) vs. 80% (4/5) vs. 14.3% (1/7) G3: 0% (0/2) vs. 0% (0/3) vs. 0% (0/3) vs 100% (2/2)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Huland, 1990[114] RCT Medium	A vs. B vs. C Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75)	NR	A vs. B vs. C vs. D Chemical cystitis: 25% vs. 12% vs. 18% vs. 48% Allergy: 2% vs. 2% vs. 1% vs. 2% Other: 6% vs. 4% vs. 10% vs. 16% Total: 33% vs. 18% vs. 29% vs. 66%	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Jimenez-Cruz, 1997[115] RCT Medium	Spain Multicenter	Recurrent histologically proved superficial transitional cell carcinoma of the bladder (Stage T1, grade 1 to 3)	Primary tumors, Stage pTa and infiltrative tumors, Previous treatment with interferon or BCG for bladder tumor	A. BCG (Pasteur F) 150mg in 50ml saline B. Interferon alpha-2a 54 MU in 50 ml saline Installations were weekly during the first month, biweekly for 2 months, and monthly for 9 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Jimenez-Cruz, 1997[115] RCT Medium	Urine cytology, bladder ultrasound and cystoscopy every 3 months for first year then every 4 months for second year; mean months of followup (21 vs 18)	Screened: Not reported Randomized: 122 (61 vs 61) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 110 (61 vs 49)	Age (mean): 67 vs 64 Male: 87% vs 82% Race: Not reported Smoking: Not reported Stage: T1: 61 vs 61 Grade: Grade 1: 51% vs 52% Grade 2: 43% vs 41% Grade 3: 7% vs 7%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Jimenez-Cruz, 1997[115] RCT Medium	Patients with recurrences 24 (39%) vs 34 (69%) Disease-free interval (mo): 93 vs 84	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Jimenez-Cruz, 1997[115] RCT Medium			Cessation of treatment due to intolerance: 4 (7%) vs 0 Dysuria, frequency, urgency: 85% vs 0 Fever: 5% vs 0	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Kaasinen, 2000[116] RCT Medium Finnbladder IV	Finland Multicenter 1992 to 1996	At least 2 histologically verified recurrent stage Ta or T1 grade 1 to 2 tumors without concomitant CIS, Grade 3 tumors also included		All patients received MMC 40 mg in 100ml of buffered solution perioperatively followed by 4 weekly MMC instillations and then randomized to (in addition to MMC): A. BCG (OncoTICE) 5 x 10^8 colony-forming units in 100 ml saline monthly B. Interferon alpha-2b in 100ml saline alternating with BCG monthly

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Kaasinen, 2000[116] RCT Medium Finnbladder IV		Screened: Not reported Randomized: 236 (118 vs 118) Post-randomization exclusions: 31 (due to randomization violations) Loss to followup: None reported Analyzed: 205 (102 vs 103)	Age (mean): 68 vs 67 Male: 72% vs 66% Race: Not reported Smoking: Not reported Stage: pTa: 97% vs 94% pT1: 3% vs 5% pTa-1: 0 vs 1% Grade: Grade 1: 64% vs 63% Grade 2: 34% vs 37% Grade 3: 2% vs 0

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Kaasinen, 2000[116] RCT Medium Finnbladder IV	Probability of nonrecurrence at 2 years: 73% vs 34% Probability of nonrecurrence at 5 years: 67% vs 22%	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kaasinen, 2000[116] RCT Medium Finnbladder IV			Cessation of instillation due to side effects: 1 vs 3 Contracted bladder: 1 vs 0	Finnish Cancer Foundation, Oreganon Teknika, Pharmacia-Upjohn, Roche and Schering Plough	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Kaasinen, 2003[117] RCT Medium	Sweden, Norway, Finland Multicenter 1992-1997	High-grade primary, secondary, or concomitant (with pTa or pT1 tumor) carcinoma in situ of the urinary bladder	CIS in other parts of the urinary tract, previous radiotherapy or systemic chemotherapy	Six weekly instillations of: A. MMC 40 mg in 50 ml saline followed by alternating instillations of BCG (Connaught) 120 mg in 50 ml sale and MMC monthly up to one year B. BCG 120 mg followed by BCG monthly for one year
Koontz, 1981[69] (prophylaxis) RCT Medium	USA Multicenter 1974-1977	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 ml distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 ml distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Kaasinen, 2003[117] RCT Medium	Cystoscopy, cytology, and biopsy of suspicious lesions every three months for two years and then according to local practice Median followup: 56 months	Screened: Not reported Randomized: 323 (195 vs 157) Post-randomization exclusions: 19 (6 vs 12) Loss to followup: None reported Analyzed: 304 (159 vs 145)	Age (mean): 71 vs 70 Male: 79% vs 82% Race: Not Reported Smoking: Not reported Primary CIS: 47 vs 44 Secondary CIS: pTa: 40 vs 35 pT1: 26 vs 22 Concomitant CIS: pTa: 17 vs 20 pT1: 21 vs 16 Grade of concurrent tumor: G1: 2 vs 1 G2: 11 vs 16 G3: 25 vs 19
Koontz, 1981[69] (prophylaxis) RCT Medium	Cystoscopy every 3 months followup: Mean not reported, 16 patients followed for <2 years (median 15 months)	Screened: Not reported Randomized: 95 Postrandomization exclusions: 2 Loss to followup: Not reported Analyzed: 93 (23 vs. 23. vs. 47)	Age (median): 65 years Male: 88% Race: Not reported Smoking status: Not reported Primary: Unclear Stage: Not reported Grade: Not reported Multifocal: Unclear Tumor size: Not reported

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Kaasinen, 2003[117] RCT Medium	Complete response at 3 months: 119/150 (75%) vs 120/145 (83%), p=0.6 Complete response at 1 year: 116/147 (79%) vs 106/136 (78%) Disease-free interval at 60 months: 41% vs 54% Death due to bladder cancer 13 vs 10	
Koontz, 1981[69] (prophylaxis) RCT Medium	% recurrence-free at 12 months: 63% vs. 69% vs. 40% (p=0.02 for A or B vs. C)	A or B vs. C % recurrence-free at 12 months Cytology positive: 56% vs. 40% Cytology negative: 69% vs. 40%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kaasinen, 2003[117] RCT Medium			Withdrawals due to AE: Not reported BCG monotherapy showed significantly higher scores for local and systemic side-effects at 3 and 12 months Contracted bladders: 9 vs 5	Nordic Cancer Union, Finnish Cancer Foundation, Connaught Laboratories Limited	
Koontz, 1981[69] (prophylaxis) RCT Medium			Leukopenia (WBC <3000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) Thrombocytopenia (platelets <100,000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) UTI: 0% (0/23) vs. 17% (4/23) vs. 0% (0/47)	Not reported	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Krege, 1996[70] RCT Medium	Germany, Multicenter 1985-1992	histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3), no intravesical chemotherapy during last 6 months or previous radiation	Primary stage pTa grade 1 tumor	A. TURBT only B. TURBT + MMC 20 mg in 50 ml saline every 2 weeks during year 1 and monthly during year 2 C. TURBT + BCG 120 mg (Connaught strain) in 50 ml saline and subcutaneous BCG 0.5 mg in the forearm weekly for 6 weeks and then monthly for 4 months
Lamm, 1991[118] RCT Medium	USA Multicenter 1983-1985	Transitional-cell carcinoma with tumors at stage Ta or T1 of any grade with two or more recurrences in the most recent 12 months, CIS, or both		A. BCG 120 mg (Connaught strain) in 50 ml saline and 0.5ml administered percutaneously to inner thigh six weekly treatments with additional single intravesical and percutaneous treatments at 3, 6, 12, 18, and 24 months B. Doxorubin 50 mg in 50 ml saline 4 weekly treatments followed by 11 monthly treatments

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Krege, 1996[70] RCT Medium	Evaluated after 3, 6, 9, 12, 18, 24, 30, and 36 months Mean followup: 20 months	Number screened: Not reported Randomized: 337 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 336 (122 vs 112 vs 102)	Age (mean): 65 (not specified by group) Male: 75% vs 84% vs 80% Race: Not reported Smoking: Not reported Stage: Ta: 95 (78%) vs 84 (74%) vs 78 (77%) T1: 27 (22%) vs 29 (26%) vs 24 (24%) Grade: Grade 1: 47 (39%) vs 40 (39%) vs 36 (41%) Grade 2: 69 (57%) vs 57 (51%) vs 57 (56%) Grade 3: 6 (5%) vs 12 (11%) vs 4 (4%)
Lamm, 1991[118] RCT Medium	Median followup: 65 months	Screened: Not reported Randomized: 285 (143 vs 142) Post-randomization exclusions: 23 patients found to be ineligible (16 vs 7) based on data or specimens available before randomization Loss to followup: None reported Analyzed: 262 (127 vs 135)	Age (mean): 67 vs 66 Male: 79% vs 85% White: 90% vs 82% Smoking: Not reported Stage: Ta: 79 (62%) vs 80 (59%) T1: 22 (17%) vs 28 (21%) Grade: Grade 1: 19 (15%) vs 25 (19%) Grade 2: 38 (30%) vs 45 (33%) Grade 3: 26 (20%) vs 38 (28%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Krege, 1996[70] RCT Medium	Recurrence: 56 46%) vs 30 (25%) vs 26 (25%)	
Lamm, 1991[118] RCT Medium	Recurrence: 78 (61%) vs 110 (81%) Mortality: 44 (35%) vs 46 (34%) Complete response in CIS: 45 (70%) vs 23 (47%), p<0.001	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Krege, 1996[70] RCT Medium			Cystitis: NR vs 16% vs 34% Hematuria: NR vs 3% vs 6% Fever: NR vs 0 vs 18	Ministry of Science and Technology, Germany	
Lamm, 1991[118] RCT Medium			Irritative bladder symptoms: 62% vs 49% Hematuria: 39% vs 27% Fever or chills: 42% vs 8%	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Lamm, 1995[119] RCT Medium	USA Multicenter Study years not reported	Histologically proven, completely resected Ta (noninvasive) or T1 (lamina propria invasive) transitional cell carcinoma and at increased risk for tumor recurrence	Stage T2 or higher tumors excluded; patient treated with agent or radiation therapy	1 to 2 weeks after tumor resection: A. Tice BCG: 5 x 10^8 CFU in 50 ml saline for 2 hours; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year B. Mitomycin C: 20 mg in 20 ml sterile water; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year
Liu, 2006[120] RCT Medium	China Number sites: NR Study years: May 1997 - February 1998	Superficial bladder carcinoma (primary or recurrent). Stages Ta or pT1; Grade G1 or G2.	No recurrence within 1 year prior to enrollment. CIS; muscle-invasive disease (stage pT2 or greater); age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Epirubicin, 80 mg (in 40 ml normal saline). Single intravesical installation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months. C: Mitomycin C, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Lamm, 1995[119] RCT Medium	Cystoscopy and urinary cytology were performed every 3 months for 2 years then every 6 months Median followup 913 days	Screened: Not reported Randomized: 469 Post-randomization exclusions: 22 patients ineligible due to inappropriate pathology, failure to demonstrate increased risk of recurrence, presence of another primary cancer, residual papillary tumors following resection, prior use of study treatment Loss to followup: Not reported Analyzed: 447 (225 vs 222)	Age (mean): 67 vs 67 Male: 82% vs 85% White: 93% vs 94% Smoking: Not reported Stage: TaT1: 86% vs 85% Grade: Grade 3: 29% vs 32% CIS: 14% vs 16%
Liu, 2006[120] RCT Medium	All patients followed-up for 5 years until June 2003. Cystoscopy and urinary cytology every 3 months X 2 years, then every 6 months X 3 years.	Screened: NR Randomized: 47 (16 vs. 15 vs. 16) Postrandomization exclusions: None Lost to followup: None Total Analyzed: 44 (14 vs. 15 vs. 15)	A vs. B vs C Age (Overall; not reported by group), mean: 62.2 ± 11.7 (range, 45 ~ 79) Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer (Overall; not reported by group): 23.4% (11/47) Stage and Grade: TaG1: 6.3% (1/16) vs. 0% (0/15) vs. 0% (0/16); TaG2: 6.3% (1/16) vs. 6.6% (1/15) vs. 6.3% (1/16); T1G1: 12.5% (2/16) vs. 26.7% (4/15) vs. 12.5% (2/16); T1G2: 75.0% (12/16) vs. 66.7% (10/15) vs. 81.3% (13/16) Functional Status: NR "There were no significant differences in patient characteristics among the 3 groups".

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Lamm, 1995[119] RCT Medium	Recurrence or death due to any cause: 44 months vs 22 months (97/191 vs 106/186) Disease worsening or death from any cause: No significant difference in time to disease worsening or death from any cause (87/191 vs 106/186) Death: 11% (25/225) vs 13% (28/222) Death due to bladder cancer: 4% (8/225) vs 5% (12/222)	
Liu, 2006[120] RCT Medium	A vs. B vs. C Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15) vs.93.3% (14/15) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15) vs.66.7% (13/15) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15) vs.80.0% (12/15) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15) vs.60.0% (9/15) p > 0.05 Mean interval to recurrence, months: 8 vs. 4 vs. 5 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15) vs. 40% (6/15), p > 0.05	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lamm, 1995[119] RCT Medium			Withdrawals due to AE: Not reported Systemic toxicity: 181 vs 80 realizations Bladder toxicity: 356 vs 234 realizations Patient refusal or physician reluctance to restart treatment: 8% vs 7%	NR	
Liu, 2006[120] RCT Medium	A vs. B [see comment] Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15) Mean interval to recurrence, months: 8 vs. 4 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15)	NR	A vs. B vs. C Only local toxicities observed; No general toxicities encountered. Any side effect: 13.6% vs. 53.3% vs. 46.7%, $p < 0.01$ Dysuria or urinary frequency/urgency: 6.3% (1/16) vs. 13.3% (2/15) vs. 12.5% (2/16) Stricture of urethra: 0% (0/16) vs. 6.7% (1/15) vs. 6.3% (1/16)	Pharmacia Ltd.	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Lundholm, 1996[121] RCT Medium Malmstrom, 1999[122] (5 year followup) Gardmark, 2007[123] (10 year followup)	Norway, Sweden Multicenter 1987-1992	Stage Ta, grades 1 to 3 or stage T1, grades 1 and 2 tumors were included provided there had been at least 3 tumor events during the prior 18 months. Patients with stage T1 grade 3 and those with primary or concomitant dysplasia or carcinoma in situ were included without having had prior tumor events, no chemotherapy during the past 6 months.	Previous or on-going intravesical treatment with Mitomycin C, BCG or radiotherapy	A. Mitomycin C 40mg in 50mL phosphate buffer B. BCG 120 mg (Danish strain) in 40mL saline Treatment for 6 weeks, monthly for up to 1 yr and every 3 months during year 2. [Crossover initiated in A to B in 38 patients and B to A in 21 patients]

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Lundholm, 1996[121] RCT Medium Malmstrom, 1999[122] (5 year followup) Gardmark, 2007[123] (10 year followup)	Cystoscopy and cytology quarterly for 3 years then every 6 months for years 4 and 5 Median followup 39 months 10 year followup: 123 months	Screened: Not reported Randomized: 261 (130 vs 131) Post randomization exclusions: 11 died shortly after randomization (5 vs 6) Analyzed:250 (125 vs 125)	Age (mean): 68 vs 69 Male: 84% vs 83% Race: Not reported Smoking status: Not reported Stage: Ta: 51 (48%) vs 53 (42%) T1: 32 (26%) vs 31 (25%) Dysplasia/Tis: 42 (34%) vs 41(33%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Lundholm, 1996[121] RCT Medium Malstrom, 1999[122] (5 year followup) Gardmark, 2007[123] (10 year followup)	Disease-free at 39 months: 43 (34%) vs 62 (49%), p<0.03 Median time to recurrence: 14.9 months vs 33.9 months Disease progression: 17 (14%) vs 16 (13%) Mortality: 11 (9%) vs 19 (15%) Died of bladder cancer: 4 (3%) vs 6 (5%) <u>10 year followup:</u> Progression: 34 (27%) vs 24 (19%) Mortality: 72 (58%) vs 68 (54%) Died of bladder cancer: 26 (21%) vs 19 (15%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lundholm, 1996[121] RCT Medium Malmstrom, 1999[122] (5 year followup) Gardmark, 2007[123] (10 year followup)			Withdrawal due to adverse events: 10 (8%) vs 16 (13%) Hematuria: 78 (63%) vs 112 (91%) Irritative bladder symptoms: 87 (71%) vs 100 (81%) Fever: 89 (72%) vs 96(78%) Sepsis:0 vs 3 (2%) Bladder contracture: 0 vs 1 (1%)	NR <u>10 year followup</u>: Linner Hagstrand Memory Foundation	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Malmström, 2002[124] RCT Medium	Europe (multinational) Number sites: 15 Study years: NR	Histologically confirmed transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Multiple tumors only. Stages Ta or T1; Grade G1 or G2. Karnofsky performance status > 70%; No other malignancy within 5 years of the study, except nonmelanoma skin cancer; Age ≥ 18 years; Not pregnant and on appropriate birth control.	Previous exposure to any interferon or mitomycin-C; Pelvic radiation or treatment with any cytotoxic, immunological or chemotherapeutic agent for benign conditions within 5 years of the study; Abnormal hepatic, renal or bone marrow function, or coagulation disorder; Serious infection or genitourinary surgery within 1 month of study; Bladder capacity < 150 mL and/or bladder obstruction with residual urine volume > 100 mL after spontaneous voiding; Chronic UTI; Previous exposure to any experimental drug within 4 weeks; Any significant medical or psychiatric illness preventing informed consent or following study procedures; History of TCC of upper tract and/or disease limited to prostatic urethra.	A: Interferon-α, 30 MU (in 30 ml sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First installation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks. B: Interferon-α, 50 MU (in 30 ml sterile water). Same procedure as A. C: Interferon-α, 80 MU (in 30 ml sterile water). Same procedure as A. D: Mitomycin-C, 40 mg (in 40 ml sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First installation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Malmström, 2002[124] RCT Medium	followup at 9 weeks and 13 weeks for all treatment groups and at 9 weeks only for control group. followup cystoscopy at week 9 for both groups. In addition, "routine" hematology, serum chemistry and urine analysis (including microscopy) were undertaken at "specific intervals".	Screened: NR Randomized: 115 (29 vs. 28 vs. 29 vs. 29) Postrandomization exclusions: 1 Lost to followup: None Total Analyzed: 110 (27 vs. 27 vs. 27 vs. 29)	A vs. B vs. C vs. D (reported for n = 115 randomized patients) Age, % ≥ 70 years (range): 17% (47-86) vs. 46% (45-85) vs. 21% (37-86) vs. 45% (48-86) Race: All Caucasian, except one Asian (male) and one Arab (male), groups not reported. Sex (male): 86% (25/29) vs. 79% (22/28) vs. 90% (26/29) vs. 86% (25/29) Smoking status: NR Recurrent bladder cancer: NR Stage/Grade: TaG1: 41% (12/29) vs. 29% (8/28) vs. 31% (9/29) vs. 21% (6/29); TaG2: 38% (11/29) vs. 43% (12/28) vs. 52% (15/29) vs. 48% (14/29); T1G1: 3% (1/29) vs. 7% (2/28) vs. 7% (2/29) vs. 10% (3/29); T1G2: 14% (4/29) vs. 21% (6/28) vs. 10% (3/29) vs. 21% (6/29) Functional Status ("Performance status"): Normal activity: 79% (23/29) vs. 82% (23/28) vs. 76% (22/29) vs. 83% (24/29); Minor signs/symptoms: 14% (4/29) vs. 14% (4/28) vs. 17% (5/29) vs. 17% (5/29); Some signs/symptoms: 3% (1/29) vs. 4% (1/28) vs. 7% (2/29) vs. 0% (0/29); No normal activity: 3% (1/29) vs. 0% (0/28) vs. 0% (0/29) vs. 0% (0/29)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Malmström, 2002[124] RCT Medium	NA	NA

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Malmström, 2002[124] RCT Medium	NA	NA	A vs. B vs. C vs. D Adverse events reported: 37% (10/27) vs. 37% (10/27) vs. 48% (13/27) vs. 55% (16/29)* Adverse events with frequency ≥ 10%, reported by treatment group: A: None B: Fever (11%); Pain (11%) C: Fever (11%); Pain (15%); Micturition frequency (11%) D: Pain (10%); Dysuria (10%); Hematuria (14%); Micturition disorder (14%); Micturition frequency (28%); UTI (10%) * Reported as "55% (26/29)"; error presumed to be with number of events.	Schering-Plough	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mangiarotti, 2008[125] RCT Medium	Italy Number of centers not reported Study years not reported	Nonmuscle invasive bladder cancer not previously treated with any chemotherapeutic or immunotherapeutic agent		A. MMC 40 mg in 50 ml saline weekly for 8 weeks then monthly for 12 months B. BCG (Tice strain) weekly for 6 weeks then monthly for 12 months
Martinez-Pineiro, 1990[126] RCT Medium 2nd interim report	Spain Number of centers not reported 1980-1988	Histologically proved superficial transitional cell carcinoma; Initially Ta or T1 tumors admitted, later only T1 cancer patients admitted	Previous treatment with any of the 3 study agents	A. Doxorubicin 50 mg in 50 ml saline B. BCG (Pasteur strain) 150 mg in 50 ml saline C. Thiotepa 50 mg in 50 ml saline First treatment within 14 days of TUR, treatments given weekly for 4 weeks, then monthly for 11 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mangiarotti, 2008[125] RCT Medium	Cytology and cystoscopy every 3 months Mean followup: 66 months vs 66 months	Screened: Not reported Randomized: 96 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 92 (46 vs 46)	Age (mean): 64 vs 64 Male: 76% vs 70% Race: Not reported Smoking: Not reported Stage: Ta: 32 (70%) vs 21 (46%) T1: 14 (30%) vs 25 (54%) Grade: Grade 1: 26 (57%) vs 31 (67%) Grade 2: 20 (43%) vs 15 (33%)
Martinez-Pineiro, 1990[126] RCT Medium 2nd interim report	Cystoscopy and cytology every 3 months for 1 year then every 4 months for 2 years and then every 6 months thereafter Median followup 3 years (range 3-97 months)	Screened: Not reported Randomized; 202 Post-randomization exclusions: None reported Loss to followup: 9 (also excluded were 1 for protocol violation and 7 for being too early) Analyzed: 176	Age (Median): 62 vs 64 vs 65 Male: 89% vs 82% vs 84% Race: Not reported Smoking: Not reported Stage: Ta: 21 (40%) vs 18 (27%) vs 23 (41%) T1: 32 (60%) vs 49 (73%) vs 33 (59%) Grade: Grade 1: 24 (45%) vs 23 (34%) vs 18 (32%) Grade 2: 18 (34%) vs 29 (43%) vs 24 (43%) Grade 3: 11 (21%) vs 15 (22%) vs 14 (25%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Mangiarotti, 2008[125] RCT Medium	Recurrence: 23 (50%) vs 23 (50%) Recurrence free interval: 27 months vs 36 months (p=0.132)	
Martinez-Pineiro, 1990[126] RCT Medium 2nd interim report	Recurrence: 23 (43%) vs 9 (13%) vs 20 (36%) Months to recurrence (mean): 31 vs 31 vs 29 Progression: 4 (8%) vs 1 (2%) vs 2 (4%) Death due to metastic disease: 1 vs 0 vs 0 Noncancer death: 0 vs 0 vs 1	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mangiarotti, 2008[125] RCT Medium			Cystitis: 10 (22%) vs 19 (41%) Gross hematuria: 2 (4%) vs 0 Fever: 0 vs 2 (4%) Treatment discontinued: 11 (24%) vs 2 (4%)	NR	
Martinez-Pineiro, 1990[126] RCT Medium 2nd interim report			Bladder irritability: 7 (13%) vs 28 (42%) vs 8 (14%) Cystitis: 0 vs 11 (16%) vs 0 Fever: 0 vs 5 (7%) vs 0 Contracted bladder: 0 vs 1 (1%) vs 0	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Matsumura, 1992[75] RCT Medium	Japan Number sites: Unclear (multicenter) July 1987 - December 1989	Transitional-cell carcinoma of the bladder. Primary (only with multiple lesions) or recurrent. Stages Tis, Ta, or T1; Grade G0, G1, G2 or G3.	None reported	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 installations over 2 years, after TURBT: Timing of first dose not specified; installations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4. B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 installations over 2 weeks before TURBT; specific schedule not reported. C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Matsumura, 1992[75] RCT Medium	240 days, overall. (n = 284) 720 days (maximum), overall, not reported by group. (n = 156) followup methods not reported.	Screened: NR Randomized: 443 (182 vs. 126 vs. 135) Postrandomization exclusions: 42 (16 vs. 13 vs. 13) Lost to followup: 26 (not reported by group) Total Analyzed: 284 (126 vs. 75 vs. 83)	A vs. B vs. C Age: ≤ 49 years: 7.1% (9/126) vs. 4.0% (3/75) vs. 12.1% (10/83); 50-59 years: 15.1% (19/126) vs. 20.0% (15/75) vs. 13.3% (11/83); 60-69 years: 34.1% (43/126) vs. 32.0% (24/75) vs. 31.3% (26/83); ≥ 70 years: 42.9% (54/126) vs. 44.0% (33/75) vs. 42.2% (35/83); age overall, p = NS Race: NR Sex (male): 81.7% (103/126) vs. 78.7% (59/75) vs. 84.3% (70/83), p = NS Smoking status: NR Recurrent bladder cancer: 59.5% (75/126) vs. 61.3% (46/75) vs. 50.6% (42/83), p = NS Stage: Ta: 32.5% (41/126) vs. 20.6% (26/75) vs. 32.5% (27/83); T1: 42.9% (54/126) vs. 20.6% (26/75) vs. 36.1% (30/83); Tis: 0.8% (1/126) vs. 2.7% (2/75) vs. 3.6% (3/83); Unknown: 23.8% (30/126) vs. 28.0% (21/75) vs. 26.5% (22/83); p = NS Grade: G0: 2.4% (3/126) vs. 8.0% (6/75) vs. 2.4% (2/83); G1: 33.3% (42/126) vs. 34.7% (26/75) vs. 32.5% (27/83); G2: 36.5% (46/126) vs. 30.7% (23/75) vs. 36.1% (30/83); G3: 4.0% (5/126) vs. 4.0% (3/75) vs. 0.0% (0/83); Unknown: 23.8% (30/126) vs. 22.7% (17/75) vs. 28.9% (24/83); p = NS Functional Status: NR Size: ≈ 1 cm: 52.4% (66/126) vs. 49.3% (37/75) vs. 55.4% (46/83); ≈ 3 cm: 34.1% (43/126) vs. 42.7% (32/75) vs. 33.7% (28/83); ≈ 5 cm: 7.1% (9/126) vs. 6.7% (5/75) vs. 7.2% (6/83); > 5 cm: 0.8% (1/126) vs. 1.3% (1/75) vs. 1.2% (1/83); Unknown: 5.6% (7/126) vs. 0.0% (0/75) vs. 2.4% (2/83); p = NS Multiplicity: Single: 26.2% (33/126) vs. 22.7% (17/75) vs. 24.1% (20/83); 2-4: 58.7% (74/126) vs. 46.7% (35/75) vs. 54.2% (45/83); ≥ 5: 11.9% (15/126) vs. 25.3% (19/75) vs. 18.1% (15/83); Unknown: 2.4% (3/126) vs. 2.7% (2/75) vs. 2.4% (2/83); p = NS

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Matsumura, 1992[75] RCT Medium	A vs. B vs. C Recurrence-free survival rate at 240 days: 73.8% vs. 57.8% vs. 61.2%; A vs. B, $p < 0.05$; other comparisons, p = NS Recurrence-free survival rate at 480 days: 52.0% vs. 37.0% vs. 32.0%; A vs. C, $p < 0.01$; other comparisons, p = NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8% vs. 17.8%; A vs. B, $p < 0.05$; A vs. C, $p < 0.01$; other comparisons, p = NS	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsumura, 1992[75] RCT Medium	A vs. B Recurrence-free survival rate at 240 days: 73.8% vs. 57.8%, p < 0.05 Recurrence-free survival rate at 480 days: 52.0% vs. 37.0%, p = NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8%, p < 0.05	NR	A vs. B (not reported for group C) Pollakiuria: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75) Contracted bladder: 0.0% (0/126) vs. 1.3% (1/75)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Melekos, 1993[78] RCT Medium	Greece Number of centers not reported Study years not reported	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Multifocal carcinoma in situ and another cancer or history of another cancer outside the bladder and who had had previous local or systemic chemotherapy or radiotherapy	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 ml saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup B. Epirubicin: 50 mg in 50 ml saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup C. TURBT alone
Melekos, 1996[127] RCT Medium	Greece Number of centers not reported Study years not reported	Completely resectable recurrent (at least 2 recurrences in the most recent 12 months) or multiple (more than 2) papillary superficial bladder tumors Ta and T1 of any grade	Solitary-primary neoplasms, stage >T1, multifocal CIS, previous systemic chemotherapy or radiotherapy	A. Epirubicin 50 mg in 50 ml saline weekly for 4 weeks beginning within 2 days of TUR B. BCG 5 x 10^8 CFU (Tice strain) in 50 ml saline weekly for 6 weeks beginning approximately 10 days after TUR Those free of recurrence then received a single maintenance dose every 3 months during the first 2 years and then every 6 months thereafter until the end of the second year of followup; for T1 or TaG2/G3 instead of a single dose at 6 months, patients received 3 weekly doses at months 3 and 6 of followup

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Melekos, 1993[78] RCT Medium	Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter Total months of followup: 1784 vs 1745 vs 603	Screened: Not reported Randomized: 190 (2:2:1) Post-randomization exclusions: 29 patients ineligible due to protocol violation, loss to followup, or other reason Analyzed: 161 (62 vs 67 vs 32)	Age (mean): 67 vs 66 vs 68 years Male: 82% vs 84% vs 84% Race: Not reported Smoking: Not reported Stage: Ta: 66% vs 63% vs 66% T1: 34% vs 37% vs 34% Grade: Grade 1: 44% vs 46% vs 41% Grade 2: 44% vs 37% vs 44% Grade 3: 13% vs 16% vs 16% Tis: 6% vs 4% vs 6%
Melekos, 1996[127] RCT Medium	Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter Median followup: 43 months vs 43 months	Screened: Not reported Randomized: 132 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 119 (61 vs 58)	Age (mean): 67 vs 65 Male: 87% vs 90% Race: Not reported Smoking: Not reported Stage: Ta: 38 (62%) vs 34 (59%) T1: 23 (38%) vs 24 (41%) Grade: Grade 1: 12 (20%) vs 12 (21%) Grade 2: 35 (57%) vs 34 (59%) Grade 3: 14 (23%) vs 12 (21%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Melekos, 1993[78] RCT Medium	Recurrence: 32% vs 40% vs 59% Interval before recurrence: 18 months vs 16 months vs 11 months Progression: 6% vs 9% vs 22% Muscle invasion: 3% vs 4% vs 13%	
Melekos, 1996[127] RCT Medium	Recurrence: 34 (56%) vs 26 (45%) Progression: 10 (16%) vs 7 (12%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1993[78] RCT Medium			Withdrawals due to AE: Not reported Cystitis:79% vs 34% vs Not reported Fever: 27% vs 3% vs Not reported Flu-like illness:13% vs 0% vs Not reported Macroscopic hematuria: 23% vs 15% vs Not reported Reduced bladder volume: 0% vs 1% vs Not reported Treatment delay: 5% vs Epi 8% vs Not reported	NR	
Melekos, 1996[127] RCT Medium			Cystitis: 38% vs 67% Macroscopic hematuria: 16% vs 24% Treatment delayed: 12% vs 5%	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mohsen, 2010[128] RCT Medium	Egypt Number of centers not reported 2003-2006	At least 2 histologically verified recurrent stage Ta or T1 during the preceding 1.5 years		A. MMC 40 mg in 50 ml saline immediately after resection and then 4 weekly instillations; then BCG 5 x 10^8 in 50 ml saline monthly for postoperative months 2 through 12 B. BCG 5 X 10^8 in 50 ml saline with no perioperative instillations, then weekly for 6 weeks then monthly for postoperative months 3 through 12
Nepple, 2010[129] RCT Medium	USA Multicenter 1999-2003	Histologically confirmed CIS, Ta, T1 urothelial cancer diagnosed within 8 weeks	Prior BCG treatment for bladder cancer	A. BCG 50 mg (TICE) 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months B. BCG 50 mg (TICE) plus INF alpha-2b 50 MU 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months Patients were also randomized to regular or mega-dose vitamins

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mohsen, 2010[128] RCT Medium	Cytology and cystoscopy every 3 months Mean followup: 24 months	Screened: Not reported Randomized: 56 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 56 (29 vs 27)	Age (mean): 48 vs 48 Male: 69% vs 67% Race: Not reported Smoking: Not reported Stage: pTa: 15 (52%) vs 14 (52%) pT1: 14 (48%) vs 13 (48%)
Nepple, 2010[129] RCT Medium	Cystoscopy and cytology every 3 months for 24 months then semiannually for 2 years then annually thereafter Followup: 24 months	Screened: Not reported Randomized: 670 (324 vs 346) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 670 (324 vs 346)	Age: 68 Male: 76% Race: Not reported Smoking: Not reported CIS: 8%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Mohsen, 2010[128] RCT Medium	Recurrence: 9 (31%) vs 16 (70%) Median time to first recurrence: 9 months vs 6 months	
Nepple, 2010[129] RCT Medium	Recurrence: 104 (32%) vs 127 (37%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mohsen, 2010[128] RCT Medium			NR	NR	
Nepple, 2010[129] RCT Medium			Constitutional symptoms: 58 (18%) vs 38 (11%) Fever: 36 (11%) vs 17 (5%)	Schering-Plough Corp and Mission Pharmacal	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	Japan Number sites: 33 Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superfical cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	5 years, maximum; Not reported as median/mean, nor for each group. Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Post-randomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Non-evaluated patients due to protocol violations, cessation of installation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (yrs), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: Not reported Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR Grade: NR Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * From Akaza, 1987[49]. No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days*: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ Not reported for other treatment group comparisons.	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Niijima, 1983[50] (see also Akaza, 1987[49]) RCT Medium	A vs. B Recurrence-free survival rate at 540 days: 56.6% vs. 52.0%	NR	A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9%	Ministry of Health and Welfare of Japan	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ojea, 2007[130] RCT Medium	Spain Multicenter 1995-1998	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	TaG1 tumors; concurrent or previous muscle-invasive disease; concurrent or previous tumor in upper urinary tract or prostatic urethra, intravesical treatment with MMC or BCG during previous 6 months; another malignancy except basal cell carcinoma of skin; previous pelvic irradiation	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. Mitomycin C: 30 mg
Oosterlinck, 2011[131] RCT Medium	Belgium, Sweden, Portugal, Italy, Turkey, the Netherlands, United Kingdom Multicenter 2001-2005	Primary, concurrent, or recurrent biopsy-proven CIS, no pretreatment with BCG and no intravesical treatment with chemotherapeutic agents within 3 months prior to TUR		15-28 days after TUR: A. MMC 40 mg in 50 ml saline weekly for six weeks followed by BCG (Tice strain 5 x 10^8 CFU in 50 ml saline) weekly for six weeks B. BCG (Tice strain 5 x 10^8 CFU in 50 ml saline) weekly for six weeks, then 3 weeks of rest, then 3 weeks of BCG Maintenance therapy for complete responders was three weekly maintenance instillations at 6, 12, 18, 24, 30 and 36 months; maintenance for group 1 was 1 MMC then 2 BCG instillations

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ojea, 2007[130] RCT Medium	Cystoscopy every 3 months during first year and then every 4 months for the next 4 years Median followup: 57 months vs 61 months vs 53 months	Screened: Not reported Randomized: 430 Post-randomization exclusion: 33 patients did not complete treatment and were withdrawn from study but were followed for recurrence and other end points Loss to followup: Not reported Analyzed: 397 (125 vs135 vs 137)	Age (mean): 65 vs 65 vs 64 Male: 88% vs 86% vs 87% Race: Not reported Smoking: Not reported Stage: TaG2: 16% vs 14% vs 9% T1G1: 22% vs 23% vs 23%
Oosterlinck, 2011[131] RCT Medium	Cystoscopy and cytology every 3 months for 3 years then every 6 months for 2 years and then yearly thereafter Median followup: 4.7 years	Screened: Not reported Randomized: 96 (48 vs 48) Post-randomization exclusions: 13 (7 vs 6) Loss to followup: Not reported Analyzed: 83 (41 vs 42)	Age (Median): 68 vs 70 Male: 92% vs 81% Race: Not reported Smoking: Not reported Stage: pTa: 17 (35%) vs 11 (23%) pT1: 10 (21%) vs 14 (29%) pTx: 0 vs 1 (2%) Missing: 0 vs 1 (2%) CIS: 5 (10%) vs 4 (8%) No papillary lesions: 21 (44%) vs 21 (44%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ojea, 2007[130] RCT Medium	Recurrence: 27% vs 36% vs 39% Progression: 10% vs 13% vs 9%	
Oosterlinck, 2011[131] RCT Medium	Complete response (ITT): 28 (58%) vs 26 (54%) Complete response (per-protocol): 25 (61%) vs 26 (62%) Progression (ITT): 1 (2%) vs 1 (2%) Progression (per-protocol): 1 (2%) vs 1 (2%) Recurrence (ITT): 23 (48%) vs 26 (54%) Mortality: 7 (15%) vs 11 (23%) Death not due to bladder cancer: 2 vs 2	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ojea, 2007[130] RCT Medium			Withdrawals due to AE: Not reported Local toxicity 65% vs 64% vs 30% Systemic toxicity: 11% vs 11% vs 5%	NR	
Oosterlinck, 2011[131] RCT Medium			Chemical cystitis: (16%) Dysuria: (24%) Fever: 9 No difference between groups Sepsis: 0 vs 1 Withdrawal due to AE: 2 vs 1	Grants from National Cancer Institute (USA), Fonds Cancer (FOCA) in Belgium and from Kyowa Hakko Ltd and Organon Teknika (now part of Merck)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Pagano, 1995[132] RCT High Bassi, 1992[133] Abstract of interim results	Italy Single Center 1990	Multiple papillary tumors (Ta-T1) and CIS		6-week course of intravesical therapy: A. BCG 75 mg B. BCG 150 mg
Porena, 2010[134] RCT Medium	Italy Single center 2004-2006	Superficial TCC; high risk superficial bladder cancer according to EAU guidelines	Concomitant tumors, UTIs, altered function	14 days after second look TURB patients received 6 weekly instillations of: A. BCG 5x10^8 CFU (Tice strain) in 50 ml of saline, maintenance therapy at 3,6,12,18,24,30, and 36 months B. Gemcitabine 2,000 mg in 50 ml; maintenance therapy at 3,6,12,18,24,30, and 36 months

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Pagano, 1995[132] RCT High Bassi, 1992[135] Abstract of interim results	Serial cystoendoscopies with multiple biopsies of normal-and abnormal-appearing bladder mucosa, from the prostatic urethra and voided and washing cytology	Screened: Not reported Randomized: Not reported Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 183 (90 vs 93)	Not reported
Porena, 2010[134] RCT Medium	In tumor free cases, urinary cytology and cystoscopy were performed every 3 months for the first 2 years then every 6 months for the following 3 years, then annually; mean followup 44 months	Screened: 74 Randomized: 64 (32 vs 32) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence 64 (32 vs 32)	Age (mean): 69 vs 70 years Male: 88% vs 81% Race: Not reported Smoking: Not reported Stage: Ta-T1 G3: 88% vs 81% T1 G3 or CIS:13% vs 19%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Pagano, 1995[132] RCT High Bassi, 1992[135] Abstract of interim results	Disease free survival Ta: no difference between doses (p=0.55) Disease free survival CIS: favors the low dose group (p<0.001) Disease free survival T1: number of patients enrolled to date does not allow a statistical conclusion (p=0.07)	
Porena, 2010[134] RCT Medium	Recurrence: 28% vs 53% (p=0.037) Interval before recurrence: 39 months vs 26 months (p=0.042) Persistence of high-risk disease: 44% vs 41% (p=NS) Progression: 0 vs 0 (p=NS)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pagano, 1995[132] RCT High Bassi, 1992[135] Abstract of interim results			Withdrawals due to AE: Not reported Fever: 18 vs 33, p<0.05 Cystitis: 32 vs 57, p<0.05 Macroscopic hematuria: 13 vs 26, p<0.05	NR	
Porena, 2010[134] RCT Medium			Withdrawals due to AE: Not reported Severe local toxicity: 13% vs 0% Moderate local toxicity: 0% vs 9% Systemic toxicity: 6% vs 0% Postpone/suspend treatment: 13% vs 0%	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	Finland Number sites: 18 Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 million units (in 100 ml physiological saline). Single intravesical installation immediately after TUR, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 ml physiological saline). Single intravesical installation immediately after TUR, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	Overall duration of study was 2 years. Mean/median followup durations not reported. Cystoscopy and urinary cytology every 3 months X 2 years.	Screened: 283 Randomized: 283 Postrandomization exclusions: 40 Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age: NR Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	A vs. B vs. C Recurrence: 63.7% (42/66) vs. 33.8% (23/68) vs. 60.6 (40/66)	A vs. B vs. C Recurrence by stage: Ta: 64.2% (34/53) vs. 35.2% (19/54) vs. 56.4% (31/55), $p < 0.05$ T1: 61.5% (8/13) vs. 28.6% (4/14) vs. 81.8% (9/11), $p < 0.01$ Recurrence by grade: G1: 51.7% (15/29) vs. 20.6% (7/34) vs. 52.6% (20/38), $p < 0.01$ G2: 70.0% (20/29) vs. 44.0% (11/25) vs. 66.7% (14/21), $p = 0.09$ G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7), p = NS Recurrence by tumor multiplicity: Single: 62.7% (32/51) vs. 26.9% (14/52) vs. 55.3% (26/47), $p < 0.01$ Multiple: 66.7% (10/15) vs. 56.3% (9/16) vs. 73.7% (14/19), p = NS

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 1999[86] (see also Rajala, 2002[87]) RCT Medium	NR	NR	A vs. B vs. C Fever: 6% (4/66) vs. 0% (0/68) vs. 1.5% (1/66) Dysuria: 1.5% (1/66) vs. 5.9% (4/68) vs. 0% (0/66)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	Finland Number sites: 18 Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 milliunits (in 100 ml physiological saline). Single intravesical installation immediately after TUR, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 ml physiological saline). Single intravesical installation immediately after TUR, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	Median followup (Overall; not reported by groups): 72 months (range 6-102). Cystoscopy and urinary cytology every 3 months X 1 year. Thereafter, followup cystoscopy according to the practice at each center.	Screened: 283 Randomized: 283 [see comment] Postrandomization exclusions: 40 [see comment] Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age, mean: 66.3 vs. 65.1 vs. 64.6 Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	A vs. B vs. C Recurrence: 68.2% (45/66) vs. 45.6% (31/68) vs. 72.7 (48/66), p = 0.002 Recurrence-free at 72 months: 31.4% vs. 50.8% vs. 23.7% Recurrence-free survival: B > A or C, p = 0.002 Median time to first recurrence, months (95% CI): 12 (9-15) vs. [not attained] vs. 9 (5-13)	A vs. B vs. C Recurrence by stage: Ta: 67.9% (36/53) vs. 46.3% (25/54) vs. 70.9% (39/55) T1: 69.2% (9/13) vs. 42.9% (6/14) vs. 81.8% (9/11) Recurrence by grade: G1: 58.6% (17/29) vs. 38.2% (13/34) vs. 65.8% (25/38) G2: 72.4% (21/29) vs. 52.0% (13/25) vs. 81.0% (17/21) G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7) Recurrence by tumor multiplicity: Single: 64.7% (33/51) vs. 42.3% (22/52) vs. 70.2% (33/47) 2 tumors: 70.0% (7/10) vs. 33.3% (3/9) vs. 83.3% (10/12) 3 tumors: 100% (3/3) vs. 80.0% (4/5) vs. 33.3% (1/3) ≥ 4 tumors: 100% (2/2) vs. 100% (2/2) vs. 100% (4/4)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 2002[87] (see also Rajala, 1999[86]) RCT Medium	NR	NR	NR	Finnish Cancer Foundation; Pharmacia; Roche and Schering-Plough	Study is followup of Rajala, 1999. Description of followup cystoscopy internal after year 1 is not consistent with Rajala, 1999. Number randomized and postrandomization exclusion taken from Rajala, 1999.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rintala, 1991[136] RCT Medium Jarvinen, 2009[137] FinnBladder I (20 year followup)	Finland Multicenter 1984-1987	Frequently recurrent TaT1 tumors and/or CISTa-T1 cancers with a minimum of two episodes of recurrence during the preceding 1.5 years	Urethral or prostatic involvement	2 weeks after TURBT 5 weekly instillations then monthly instillations up to 2 years of: A. MMC dose and volume adjust for bladder capacity but averaged 30-40 mg in 150-200 ml phosphate buffer B. BCG 75 mg (Pasteur strain F)
Rintala, 1995[138] RCT Medium Jarvinen, 2012[139] FinnBladder II with 17 year followup of CIS	Finland Multicenter 1987-1992	Primary, secondary, or concomitant CIS	Ta or T1	MMC perioperatively then 4 weekly instillations of MMC then randomized to: A. MMC monthly monotherapy B. MMC alternated with BCG monthly (Pasteur strain F 75 mg in 50 ml saline) MMC dose and volume of phosphate buffer were adjusted according to bladder capacity

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rintala, 1991[136] RCT Medium Jarvinen, 2009[137] FinnBladder I (20 year followup)	Cytology and cystoscopy every 3 months for first 2 years then between 6 and 12 months thereafter according to clinician judgment; mean followup 28 months <u>20 year followup of TaT1:</u> median followup overall 8.5 years; median followup of 17 patients still alive 19.4 years	Screened: Not reported Randomized: 109 (7 patients randomized to BCG but tested PPD-negative were transferred, according to protocol to the MMC group; 23 patients with persistent disease at 6 months were transferred to the second-line instillation (at least 8 MMC patients and 10 BCG patients were transferred) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: Unclear but at least 85 (41 vs 44) <u>20 year followup:</u> Analyzed: 89 patients with TaT1 disease without CIS (45 vs 44)	Age (mean) 67 vs 68 Male: 71% vs 76% Race: Not reported Smoking: Not reported Stage: TIS: 12 (21%) vs 6 (12%) Ta-T1: 46 (79%) vs 45 (88%) Grade: Grade 1: 33 (57%) vs 35 (69%) Grade 2: 19 (33%) vs 12 (24%) Grade 3: 6 (10%) vs 4 (8%) <u>20 year followup of TaT1:</u> Age (mean) 67 vs 68 Male: 67% vs 77% Stage: Ta: 29 (64%) vs 31 (70%) T1: 4 (9%) vs 3 (7%) Grade: Grade 1: 13 (29%) vs 16 (36%) Grade 2: 19 (42%) vs 17 (39%) Grade 3: 1 (2%) vs 1 (2%)
Rintala, 1995[138] RCT Medium Jarvinen, 2012[139] FinnBladder II with 17 year followup of CIS	Cytology and cystoscopy every 3 months for first 2 years and then annually or according to clinician's decision; mean followup 33 months <u>17 year followup of CIS:</u> median followup 7.2 years	Screened: Not reported Randomized (subgroup): 68 (40 vs 28) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 68 (40 vs 28)	Age (mean): 68 vs 66 Male: 78% vs 86% Race: Not reported Smoking: Not reported Primary CIS: 15 (38%) vs 15 (54%) Secondary CIS: 15 (38%) vs 2 (7%) Concomitant CIS: 10 (25%) vs 11 (39%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rintala, 1991[136] RCT Medium Jarvinen, 2009[137] FinnBladder I (20 year followup)	TIS Complete response: 12 (58%) vs 10 (40%) TaT1 Complete response at 6 months: 70% vs 88% TaT1 Complete response at 12 months: 67% vs 90% TaT1 Complete response at 2 years: 79% vs 97% <u>20 year followup of TaT1</u>: Recurrence: 36 (80%) vs 26 (59%) Progression: 10 (22%) vs 4 (9%) Died from bladder cancer: 9 (20%) vs 4 (9%) Overall mortality: 80% vs 82%	
Rintala, 1995[138] RCT Medium Jarvinen, 2012[139] FinnBladder II with 17 year followup of CIS	Complete response 3 months: 45% vs 71%, p=0.047 Complete response 6 months: 50% vs 75%, p=0.047 Complete response 12 months: 59% vs 82%, 0.062 Complete response 24 months: 47% vs 74%, p=0.041 Progression: 4 vs 2 <u>17 year followup of CIS:</u> Recurrence: 35 (88%) vs 19 (68%), p=0.06 Progression: 14 (35%) vs 8 (28%), p=0.59 Died from bladder carcinoma: 12 (30%) vs 8 (29%) Overall mortality: 30 (75%) vs 20(71%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rintala, 1991[136] RCT Medium Jarvinen, 2009[137] FinnBladder I (20 year followup)			Instillations discontinued due to side effects: 2 (9%) vs 9 (20%)	Finnish Cancer Foundation, Academy of Finland Paolo Foundation, Research and Science Foundation of Farmos 20 year followup of TaT1: Funding/support and role of the sponsor: None	
Rintala, 1995[138] RCT Medium Jarvinen, 2012[139] FinnBladder II with 17 year followup of CIS			Chemical cystitis: 1 vs 0 Bladder contraction: 1 vs 0	Finnish Cancer Foundation, Academy of Finland and Paulo Foundation	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rintala, 1996[140] RCT Medium FinnBladder II	Finland Multicenter 1987-1992	recurrent stage Ta or T1 papillary transitional cell carcinoma		MMC perioperatively then 4 weekly instillations of MMC then randomized to: A. MMC monthly monotherapy B. MMC alternated with BCG monthly (Pasteur strain F 75 mg in 50 ml saline) MMC dose and volume of phosphate buffer were adjusted according to bladder capacity
Rubben, 1988[141] Medium	Germany Single center 1979-1981	Primary or recurrent NMIBC, any grade	Bimanual palpable tumor after TURBT, previous radiotherapy, intravesical chemotherapy within 6 months, other malignancy	A: Doxorubicin 50 mg/50 ml saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) B: Doxorubicin 50 mg/50 ml saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rintala, 1996[140] RCT Medium FinnBladder II	Cytology and cystoscopy every 3 months for first 2 years and then annually or according to clinician's decision; mean followup 34 months but focus is on 2-year instillation period	Screened: Not reported Randomized (subgroup): 188 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 182 (90 vs 92)	Age (mean): 69 vs 68 Male: 76% vs 75% Race: Not reported Smoking: Not reported Grade: Grade 1: 49 (53%) vs 55 (58%) Grade 2: 40 (43%) vs 39 (41%) Grade 3: 4 (4%) vs 1 (1%)
Rubben, 1988[141] Medium	Cystoscopy and cytology every 3 months for 2 years, then every 6 months followup: Median not reported	Screened: Not reported Randomized: 268 (91 vs. 88 vs. 89) Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 220 (79 vs. 59 vs. 82)	Age (mean): 64 vs. 64 vs. 68 years Male: 79% vs. 79% vs. 77% Race: Not reported Smoking status: Not reported Primary: 75% vs. 67% vs. 74% Recurrent: 25% vs. 33% vs. 26% Ta: 84% vs. 81% vs. 77% T1: 16% vs. 19% vs. 23% G1: 60% vs. 65% vs. 59% G2: 36% vs. 28% vs. 34% G3: 7.0% vs. 4.0% vs. 7.2% >3 cm: 19% vs. 15% vs. 24% Solitary: 69% vs. 66% vs. 82%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Rintala, 1996[140] RCT Medium FinnBladder II	Patents with recurrence: 58 (64%) vs 57 (62%) Median time to first recurrence: 12.4 months vs 6.9 months Median time to treatment failure: 30 months vs 28 months Progression based on muscle infiltration or metastases: 3 vs 3	
Rubben, 1988[141] Medium	All-cause mortality: 6.7% vs. 1.8% vs. 13.3% (p>0.35) Bladder cancer mortality: 5.3% vs. 1.8% vs. 7.2% (p>0.35) Recurrence rate: 2.5 vs. 2.3 vs. 2.7 per 100 patient-months (p>0.35) Progression: 16% vs. 11% vs. 12% (p>0.35) Time to recurrence (months): 19 vs. 22 vs. 19 (p>0.1)	Recurrence rate (per 100 patient-months) (p>0.05 in all subgroups) Primary: 2.5 vs. 2.4 vs. 2.3 Recurrent: 2.6 vs. 2.8 vs. 3.9 Solitary: 1.8 vs. 3.0 vs. 2.0 Multiple: 3.6 vs. 3.6 vs. 4.6 <3 cm: 1.9 vs. 3.4 vs. 2.9 >3 cm: 2.7 vs. 2.9 vs. 2.6 Tis negative: 2.3 vs. 3.1 vs. 2.2 Tis positive: 3.2 vs 3.2 vs. 4.4

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rintala, 1996[140] RCT Medium FinnBladder II			Discontinued installations due to side effects: 6 vs 6	Finnish Cancer Foundation, Academy of Finland and Paulo Foundation	
Rubben, 1988[141] Medium			Systemic side effects: None observed Local side effects resulting in incomplete treatment: 11% vs. 33% vs. 11%	Not reported	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Saika, 2010[88] RCT Medium	Japan Number of sites: 25 Study years: April 1995 - January 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥ 20 years.	Concurrent or previous CIS; Concurrent or previous urinary tract cancer; Concurrent or previous muscle invasive disease; Lethal disease.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (< 1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.
Sengiku, 2013[142] RCT Medium	Japan Single Center 2004-2012	Stage Ta/T1 or Tis, multiple tumors and recurrence-free period of 3 months or less		At least 2 weeks after removing as much of visible lesion as possible by TURBT, patients received weekly up to 8 times: A. BCG 80 mg (Tokyo strain) in 40 ml saline B. BCG 81 mg (Connaught strain) in 40 ml saline

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Saika, 2010[88] RCT Medium	A vs. B vs. C Median followup, overall: 44 months (range 1-70 months) Median followup, months, by group: 44 vs. 46 vs. 42 Cystoscopy every 3 months for 2 years and every 6 months thereafter.	Screened: NR Randomized: 303 Postrandomization exclusions: 21 Eligible: 257 (83 vs. 90 vs. 84) Lost to followup: 17 Total analyzed: 240 (79 vs. 84 vs. 77)	A vs. B vs. C (based on eligible patents, n = 257) Median age, years: 69 vs. 69 vs. 71 Sex (male): 81% (67/83) vs. 89% (80/90) vs. 88% (74/84) Race: NR Recurrent bladder cancer: 40% (33/83) vs. 43% (39/90) vs. 40% (34/84) Stage Ta: 54% (45/83) vs. 60% (54/90) vs. 64% (54/84) Stage T1: 46% (36/83) vs. 40% (36/90) vs. 36% (30/84) Grade G1: 25% (21/83) vs. 33% (30/90) vs. 31% (26/84) Grade G2: 59% (49/83) vs. 47% (42/90) vs. 52% (44/84) Grade G3: 14% (12/83) vs. 20% (18/90) vs. 17% (14/84) Functional status: NR
Sengiku, 2013[142] RCT Medium	Cystoscopy and urine cytology every 3 months for first 2 years and every 3-6 months thereafter	Screened: Not reported Randomized: 178 Post-randomizations exclusions (for efficacy): 49 with a history of intravesical BCG therapy or concurrent upper urinary tract tumor or discontinued BCG therapy before 6 doses were excluded Loss to followup: none reported Analyzed: 129: (66 vs 63)	Age (mean): 70 vs 71 Male: 89% vs 76% Race: Not reported Smoking: Not reported Stage: Ta: 45% vs 43% T1: 33% vs 33% Tis: 21% vs 24% Grade: High: 61% vs 57% Low: 39% vs 43% CIS: 26% vs 8%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Saika, 2010[88] RCT Medium	A vs. B vs. C Median recurrence-free survival, months: 24 vs. 38 vs. 13; A vs. B, p = 0.48; A vs. C, p=0.25; B vs. C, p=0.05 Progression: 0.0% (0/83) vs. 1.1% (1/90) vs. 0.0% (0/84)	NR
Sengiku, 2013[142] RCT Medium	Complete response for curative intent in Tis/CIS patients: 28 (90%) vs 17 (85%), p=0.90 2-Year Recurrence free survival in patients given BCG for prevention of recurrence or when complete response occurred regardless of CIS: 73% vs 69% 5-Year Recurrence free survival in patients given BCG for prevention of recurrence or when complete response occurred regardless of CIS: 62% vs 56%, p=0.75	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Saika, 2010[88] RCT Medium	NR	NR	A vs. B (not reported for group C) Local: Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p = 0.106 Systemic: Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)	NR	
Sengiku, 2013[142] RCT Medium			Withdrawals due to AE: 7 (8%) vs 9 (10%) Fever AE or complication events: 12 vs 10 Cystitis AE or complication events: 33 vs 28 Hematuria AE or complication events: 8 vs 12	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Shuin, 1994[143] RCT High	Japan Number of sites: 23 Study years: April 1990 - December 1993	Recurrent superficial bladder cancer (recurrent only). Stages Ta or T1; Grade G1 or G2.	None reported	A: Epirubicin, 30 mg (in 40 mL saline), retained in bladder for at least 2 hours. Timing of first installation not specified. Installations every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline), retained in bladder for at least 2 hours. Timing of first installation not specified. Installations every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Shuin, 1994[143] RCT High	Overall duration of study was 43 months. Mean/median followup durations not reported. followup method not described.	Screened: NR Randomized: 68 (33 vs. 35) Postrandomization exclusions: 3 (1 vs. 2) Lost to followup: NR Total analyzed: 65 (32 vs. 33)	A vs. B Age: < 40 years: 6% vs. 3% 40-49 years: 3% vs. 9% 50-59 years: 9% vs. 24% 60-69 years: 25% vs. 21% ≥ 70: 56% vs. 42%, chi-square test for age, p = NS Race: NR Sex (male): 81% (26/32) vs. 82% (27/33), p = NS Smoking status: NR Recurrent bladder cancer: 100% (recurrent only) Stage Ta: 69% (22/32) vs. 64% (21/33) Stage T1: 25% (8/32) vs. 27% (9/33) Stage unknown: 6% (2/32) vs. 9% (3/33), chi-square test for stage, p = NS Grade G1: 50% (16/32) vs. 39% (13/33) Grade G2: 59% (19/32) vs. 61% (20/33), chi-square test for grade, p = NS Functional status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Shuin, 1994[143] RCT High	A vs. B Recurrence: 25% (8/32) vs. 27% (9/33), chi-square test, p = NS Recurrence-free period, mean (range): 9.7 months (4 to 17) vs. 8.5 months (3 to 16), "no significant difference" (type of statistical testing and p-value not specified). Progression: "There has been no case of grade G3 or invasive cancer in either group."	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Shuin, 1994[143] RCT High	NR	NR	A vs. B Pollakisuria: 16% (5/32) vs. 6% (2/33), chi-square test, p = NS Dysuria: 16% (5/32) vs. 6% (2/33), chi-square test, p = NS Hematuria: 13% (4/32) vs. 6% (2/33), chi-square test, p = NS	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Tolley, 1996[91] RCT Risk of Bias: Medium (followup of Tolley, 1988[92])	United Kingdom Number of sites: 17 Study years: March 1984 - December 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	CIS alone	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes. B: Mitomycin C 40 mg (in 40 mL water), installation within 24 hours of TURBT; retained for 60 minutes. Additional installations (same dose) every 3 months x 1 year (total 5 installations). C: No adjuvant treatment. TURBT alone.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Tolley, 1996[91] RCT Risk of Bias: Medium (followup of Tolley, 1988[92])	Median followup (A and B, not reported for C): 7 years Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: 502 Randomized: 452 Postrandomization exclusions: NR Lost to followup: 5* (2 vs. 1 vs. 2) Total analyzed: 452 (149 vs. 146 vs. 157) * reportedly with no followup data, but included in ITT analyses	**A vs. B vs. C** Age 24-50: 13% (19/149) vs. 9% (13/146) vs. 9% (14/157) Age 51-60: 24% (36/149) vs. 23% (33/146) vs. 29% (46/157) Age 61-70: 36% (54/149) vs. 37% (54/146) vs. 34% (53/157) Age 71-80: 23% (34/149) vs. 30% (44/146) vs. 25% (40/157) Age 81-100: 4% (6/149) vs. 1% (2/146) vs. 3% (2/157) Male sex: NR Race: NR Smoking status: NR Stage Ta: 50% (75/149) vs. 52% (76/146) vs. 56% (88/157) Stage T1: 48% (72/149) vs. 50% (73/146) vs. 43% (67/157) Grade 1: 37% (55/149) vs. 34% (50/146) vs. 45% (71/157) Grade 2: 52% (77/149) vs. 55% (81/146) vs. 46% (73/157) Grade 3: 10% (15/149) vs. 10% (15/146) vs. 8% (13/157) Functional status: NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Tolley, 1996[91] RCT Risk of Bias: Medium (followup of Tolley, 1988[92])	**A vs. B vs. C** Annual recurrence rate (positive cystoscopies) during first 2 years: 0.42 vs. 0.31 vs. 0.82; A vs. C, p=0.001; B vs. C, p<0.001; A vs. B, p = 0.14 Recurrence, relative risk, HR (95% CI): A vs. C (ref): 0.66 (0.48 to 0.91), log-rank test, p = 0.01; B vs. C (ref): 0.50 (0.36 to 0.70), log-rank test, p = 0.0001; A vs. B (ref): 0.74 (0.51 to 1.06), log-rank test, p = 0.10 Progression, relative risk, HR (95% CI): A vs. C: 0.84 (0.42 to 1.52), log-rank test, p = 0.64; B vs. C: 0.82 (0.40 to 1.68), log-rank test, p = 0.59; A vs. B: 0.97 (0.46 to 2.06), log-rank test, p = 0.94 All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146) vs. 32.5% (51/157); A+B vs. C, HR 1.1 (95% CI 0.80 to 1.53) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146) vs. 7.6% (12/157)	NR

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Tolley, 1996[91] RCT Risk of Bias: Medium (followup of Tolley, 1988[92])	NR	NR	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was not reported as a side effect by any patient in either group.	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Europe Multicenter 1992-1997	Intermediate or high risk superficial bladder tumors; single or multiple, primary or recurrent, completely resectable stages Ta-T1, G1 to G3, biopsy proven TCC	Primary solitary tumor, T2 or greater, CIS, age>85, previously treated with doxorubicin, epirubicin, or BCG, intravesical treatment during previous 3 months	A. Epirubicin 50 mg in 50 ml saline weekly for 6 consecutive weeks starting within 24 hours of transurethral resection B. BCG 5x10^8 CFU (Tice strain) for 6 consecutive weeks starting 7-15 days after transurethral resection C.BCG + isoniazid: BCG 5x10^8 CFU (Tice) for 6 consecutive weeks starting 7-15 days after transurethral resection plus 300 mg INH orally the day before, same day and day after instillation

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Cystoscopy and urine cytology every 3 months during first 3 years and then every 6 months Median duration of treatment: 12 months vs 18 months vs 12 months Median followup: 4 years <u>Median followup:</u> 9 years	Screened: Not reported Randomized: 957 Post-randomization exclusions: 120 (32 had no tumor, 31 had muscle invasive tumor, 37 had CIS, 20 ineligible for other reasons) Loss to followup: 169 prematurely stopped treatment due to concomitant disease, refusal or loss to followup. In another 137 patients further followup data were required Analyzed: 837 (279 vs 281 vs 277)	Age (mean): 67 vs 66 vs 66 Male: 79% vs 75% vs 78% Race: Not reported Smoking: Not reported Stage: Ta: 63% vs 60% vs 63% T1: 33% vs 37% vs 35% Grade: Grade 1: 38% vs 37% vs 36% Grade 2: 48% vs 47% vs 49% Grade 3: 11% vs 13% vs 12%

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Recurrence at 3 years: 51% vs 35% vs 36% Time to first recurrence at 3.5 years: BCG with or without INH significantly prolonged time to first recurrence vs Epirubicin Progression to muscle invasive disease: 7% (19/279) vs 3% (9/281) vs 5% (15/277) Death at 3.9 years: 19% vs 15% vs 19% Death due to bladder cancer: 4% vs 2% vs 3% <u>9 year followup:</u> Recurrence: 53% vs 37% vs 40% Progression: 9% vs 7% vs 8% Death: 38% vs 30% vs 32% Death due to bladder cancer: 7% vs 3% vs 4% With BCG arms pooled (epirubicin vs BCG) hazard ratios (combines intermediate and high risk: Recurrence: 0.62 (0.50 to 0.76) Progression: 0.84 (0.51 to 1.39) Death: 0.76 (0.59 to 0.96) Death due to bladder cancer: 0.47 (0.25 to 0.89)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)			Withdrawals due to AE: 16 (6%) vs 31 (12%) vs 44 (17%) Bacterial cystitis: 26% vs 26% vs 23% Chemical cystitis 31% vs 42% vs 45% Macroscopic hematuria: 17% vs 35% vs 30%	National Cancer Institute	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147]	The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Previous local or systemic cancer therapy or radiotherapy	A. MMC 30mg in 50ml saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50ml saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147]	Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter median followup: 32 months	Screened: Not reported Randomized: 469 (156 vs 154 vs 159) Post-randomization exclusions: 17 (ineligible) Loss to followup: None reported although 15 patients excluded for "different reasons" Analyzed: 437 (148 vs 140 vs 149)	Age (mean): 66 vs 66 vs 66 Male: 80% vs 86% vs 87% Race: Not reported Smoking status: Not reported G1: 24 (16%) vs 28 (20%) vs 32 (22%) pTaG2: 55 (37%) vs 48 (34%) vs 54 (36%) G3: 4 (4%) vs 5 (4%) vs 4 (3%) CIS: 12 (8%) vs 23 (16%) vs 15 (10%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial	% Disease-free, all papillary tumors 1 yr: 76% vs 68% vs 69% 2 yr: 65% vs 54% vs 62% % Disease-free, grade 3 papillary tumors 1 yr: 79% vs 55% vs 64% 2 yr: 0 vs 46% vs 50% Complete response in patients with CIS (N=50) 5 (42%) vs 16 (70%) vs 7 (47%), p=0.20	
Witjes, 1996[147]	<u>5 year followup:</u> % Disease-free (all papillary tumors): 57% vs 36% vs 54% Response rate (CIS): 8 (67%) vs17 (74%) vs 9 (60%) Recurrence: 58/136 (43%) vs 75/117 (64%) vs 62/134 (46%)	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147]			Drug-induced cystitis: 26 (18%) vs 42 (30%) vs 48 (32%), p=0.009 Systemic side-effects: 6 (4%) vs 38 (27%) vs 27 (18%) Sepsis: 0 vs 1 vs 0 Withdrawals due to AE: 14 (total) Intercurrent death=10 (total)	NR	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Witjes, 1998[148] RCT Medium	The Netherlands Multicenter 1991-1993	Histologically proved primary multiple (more than 2 tumors) or recurrent multiple (2 or more tumors) stage pTa or pT1 transitional cell carcinoma, solitary or multiple grade III tumors and primary or concomitant CIS	Previous radiotherapy, intravesical or systemic chemotherapy within 3 months of the study	A. MMC 40 mg in 50 ml saline weekly for 4 weeks followed by BCG (Tice strain) 5 x 10^8 in 50 ml saline weekly for 6 weeks B. MMC 40 mg in 50 ml saline weekly for 10 weeks

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Witjes, 1998[148] RCT Medium	Cystoscopy and cytology every 3 months until recurrence Median followup: 32 months (range 2-65 months)	Screened: Not reported Randomized 182 (90 vs 92) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 182 (90 vs 92)	Age: Not reported Male: Not reported Race: Not reported Smoking: Not reported Stage: pTa: 43 (48%) vs 36 (39%) pT1: 36 (40%) vs 47 (51%) Grade: Grade 1: 19 (21%) vs 16 (17%) Grade 2: 42 (47%) vs 44 (48%) Grade 3: 18 (20%) vs 24 (26%) CIS: 29 (32%) vs 36 (39%)

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Witjes, 1998[148] RCT Medium	Recurrence: 35 (39%) vs 42 (46%), p=0.36 Progression: 5 (6%) vs 4 (4%), p=0.70 Mortality: 21 (23%) vs 14 (15%), p=0.16 Disease-related mortality: 5 vs 8	

Appendix E3. Key Question 3: Included Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Witjes, 1998[148] RCT Medium			Chemical cystitis: 37 (41%) vs 29 (32%) Fever (occurrences): 11 vs 3 Patients without side effects: 29 (32%) vs 38 (41%)	NR	

AE, Adverse Events; BC, Bladder Cancer; BCG, Bacillus Calmette Guerin; CFU, Colony Forming Unit; CI, Confidence Interval; CIS, carcinoma in situ; cm, centimeter; DNA, Deoxyribonucleic acid; EAU guidelines, European Association of Urology Guidelines; ECG, electrocardiography; Epi, Epirubicin; FOCA, Fonds Cancer; G1, Grade 1; G2, Grade 2; G3, Grade 3; GEM, Gemcitabine; IA, intra-arterial; IFN, Interferon; INH, isoniazid; ITT, intention-to-treat analysis; IU, International unit; IV, intravenous; IVU, intravenous urogram; mA, milliamps; mg, milligram; MIBC, Muscle Invasive Bladder Cancer; min, minute(s); ml, milliliter; mL, milliliter; MMC, Mitomycin C; mo(s), month(s); MU, Million units; NaCl, Sodium Chloride; NMIBC, Non-Muscle Invasive Bladder Cancer; NR, Not Reported; NS, Not significant; PPD, purified protein derivative; pT1, Tumor stage 1 determined by pathology; pT2, Tumor stage 2 determined by pathology; pTa, Tumor stage a determined by pathology; pTa/1, Tumor stage a/1 determined by pathology; pTis, Tumor in situ determined by pathology; pTx, Unknown tumor stage; RCT, Randomized Controlled Trial; RR, Relative risk; SD, Standard deviation; T1, Tumor stage 1; T2, Tumor stage 2; Ta, Tumor stage a; TCC, Transitional cell carcinoma; Tis, carcinoma in situ; TUR, Transurethral resection; TURB, Transurethral resection of bladder; TURBT, Transurethral resection of bladder tumor; USA, United States of America; UTIs, Urinary Tract Infections; WBC, White blood cells; yr(s), year(s)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987[49] RCT (Also Akaza, 1992[51]) Study Two Medium	Japan Number sites: Unclear Study years: July 1982 - 1985	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	Egypt Single Center Study years: June 1991 - May 1995	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function.	A: Epirubicin, 50 mg (in 50 ml normal saline). B: Epirubicin, 80 mg (in 50 ml normal saline). C: Doxorubicin, 50 mg (in 50 ml normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First installation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Installations once a week X 8 weeks, then once monthly to complete 1 year of treatment.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987[49] RCT (Also Akaza, 1992[51]) Study Two Medium	Duration: 3.5 years, maximum; Mean, median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals throughout study period	Screened: NR Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148)	A vs. B vs. C vs. D Age (yrs), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male: 80.1% vs. 82.3% vs. 82.0% vs. 81.1% Race: NR Smoking status: NR Recurrent bladder cancer: 19.7% vs. 17.7% vs. 18.0% vs. 18.9% Stage: NR Grade: NR Functional Status: NR Size: >3 cm: 14.6% vs. 11.4% vs. 11.3% vs. 6.8% Proportion with single tumor: 64.2% vs. 55.7% vs. 55.3% vs. 66.9%
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	Duration, mean: 30.1 months Method: Cystourethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter.	Screened: NR Randomized: 253 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 253 (64 vs. 68 vs. Total analyzed for dose comparison: 132 (64 vs. 68 vs. 60 vs. 61)	A vs. B vs. C vs. D Age: NR Race: NR Male: 81.4%, not reported by treatment group Smoking status: NR Recurrent bladder cancer: 37.5% vs. 41.2% vs. 43.3% vs.45.9% Stage: pTa: 10.9% vs. 17.6% vs. 6.7% vs.9.8%; pT1: 89.1% vs. 82.4% vs. 93.3% vs.90.2%; Tis associated: 6.3% vs. 11.8% vs. 0.0% vs.0.0% Grade: G1: 9.4% vs. 16.2% vs. 16.7% vs.19.7%; G2: 78.1% vs. 69.1% vs. 70.0% vs.65.6%; G3: 12.5% vs. 14.7% vs. 13.3% vs.14.7% Functional Status: NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Akaza, 1987[49] RCT (Also Akaza, 1992[51]) Study Two Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1 vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, p < 0.05 B > D, p < 0.05 C > D, p < 0.05 Long-term (median, 6.6 years) followup in subgroup of 158 patients Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31); RR 1.40 (95% CI 0.79 to 2.45) for A vs. B	NR
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	A vs. B Recurrence: 25.0% (16/64) vs. 17.6% (12/68), RR 1.42 (95% CI 0.73 to 2.76) Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4). Recurrence rate per 100 patient-months: 0.83 vs. 0.60, p < 0.05. Progression: 10.9% (7/64) vs. 4.4% (3/68), RR 2.5 (95% CI 0.67 to 9.2) Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44)	A vs. B Recurrence Ta: 0.0% (0/16) vs. 0.0% (0/12) T1: 93.8% (15/16) vs. 83.3% (10/12) Tis: 6.3% (1/16) vs. 16.7% (2/12) G1: 0.0% (0/16) vs. 16.7% (2/12) G2: 75.0% (12/16) vs. 58.3% (7/12) G3: 25.0% (4/16) vs. 25.0% (3/12) T1/G3: 66.7% (4/6) vs. 37.5% (3/8)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Akaza, 1987[49] RCT (Also Akaza, 1992[51]) Study Two Medium	A vs. B Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 Recurrence-free survival rate at 2 years: 62.3% vs. 59.1	NR
Ali-El-Dein, 1997[94] (J Urol) RCT Medium		NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987[49] RCT (Also Akaza, 1992[51]) Study Two Medium	A vs. B vs. C (not reported for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	
Ali-El-Dein, 1997[94] (J Urol) RCT Medium	A vs. B vs. C (No data for group D) Any adverse event: 15.6% (10/64) vs. 23.5% (16/68) Adverse events per # of installations: 7.3% (88/1199) vs. 8.7% (111/1280) Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) UTI: 10.0% (1/10) vs. 0.0% (0/16)	NR	Note: Possible overlap of some study subjects (group A) with those in Ali-El-Dein, 1997 (British J Urol)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	Egypt Single Center Study years: January 1992 - February 1996	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). G2 or G3, multiple recurrent, pT1, aneuploidy, or ≥3 cm; pTa if multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function; CIS.	A: Epirubicin, 50 mg (in 50 ml normal saline); Single instillation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 ml normal saline); Initial instillation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, instillations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	Duration, mean: 32.2 months Method: Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years.	Screened: 181 Randomized: 179 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 168 Per Group Analyzed (A vs. B vs. C): 55 vs. 59 vs. 54	A vs. B vs. C Age, mean years: 52.1 vs. 55 vs. 53.4 Race: NR Sex (male): 67.3% vs. 74.6% vs. 70.4% Smoking status: NR Recurrent bladder cancer: 47.2% vs. 52.5% vs. 44.4%, p = 0.5 Stage: pTa: 16.3% vs. 25.4% vs. 18.5%; pT1: 83.7% vs. 74.6% vs. 81.5%, p = 0.4. Grade: G1: 10.9% vs. 18.6% vs. 25.9%; G2: 54.5% vs. 55.9% vs. 53.7%; G3: 34.5% vs. 25.4% vs. 20.4%, p = 0.2. Functional Status: NR Size: ≥ 3 cm: 35% (19/55) vs. 29% (17/59) vs. 37% (20/54)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B Recurrence: 23.6% (13/55) vs. 25.4% (15/59), p = 0.8. Mean interval to first recurrence, months: 16 vs. 18 Recurrence rate per 100 patient-months: 0.79 vs. 0.84 Progression: 5.5% (3/55) vs. 3.4% (2/59)	A vs. B Recurrence Ta: 0.0% (0/9) vs. 0.0% (0/15) T1: 28.3% (13/46) vs. 34.1% (15/44) G1: 0.0% (0/6) vs. 27.3% (3/11) G2: 10.0% (3/30) vs. 27.3% (9/33) G3: 52.6% (10/19) vs. 20.0% (3/15), RR 2.63 (95% CI 0.88 to 7.89) ≥ 3 cm: 21.1% (4/19) vs. 41.2% (7/17), RR 0.51 (95% CI 0.18 to 1.45)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium		NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997[52] (British J Urol) RCT Medium	A vs. B Any adverse event: 21.8% (12/55) vs. 25.4% (15/59), p = 0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15) , p = 0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p = 0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.	No financial support received	Note: Possible overlap of some study subjects (group B) with those in Ali-El-Dein, 1997 (J Urol)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Au, 2001[149] RCT Medium	USA, Europe, and Canada Multicenter 1992-2000	Transitional cell carcinoma of bladder at high risk for recurrence based on 1) two or more episodes of Ta, Tis, or T1 cancers, 2) multifocal (≥3 papillary tumors or Tis involving ≥25% of bladder surface and/or in two or more biopsy sites), 3) tumors >5 cm, G3, or DNA aneuploidy	Treatment with mitomycin C within 56 weeks, prior T2-T4 bladder cancer, concurrent cancer, pregnant, WBC <4000/mm3, platelets <100,000/mm3, Cr ≥2.0 mg/dL, Karnofsky performance score <50	A: Mitomycin C 40 mg/20 ml sterile water, 6 instillations (once weekly for 6 weeks), optimized by instruction to refrain from fluids for 8 hour prior to and during instillations, oral doses of 1.3 g sodium bicarbonate the night before, Foley to empty bladder prior to instillation for post void residual <10 ml B: Mitomycin C 20 mg/20 ml sterile water, 6 instillations (once weekly for 6 weeks), without additional optimization measures

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Au, 2001[149] RCT Medium	Duration: 5 years Method: Cystoscopy and cytology every 3 months for 2 years, every 6 months for years 3-5, and once yearly thereafter	Screened: Not reported Randomized: 230 (119 vs. 111) Postrandomizations exclusions: 29 (17 vs. 12) Loss to followup: 2 (1 vs. 1) Analyzed: 201 (102 vs. 99)	Age (median): 68 vs. 65 Male: 74% vs. 75% White race: 93% vs. 95% Smoking status: Not reported Ta: 64% vs. 68% T1: 28% vs. 22% CIS: 8.4% vs. 9.9% G1/2: 75% vs. 75% G3: 25% vs. 25% Unifocal: 44% vs. 43% Primary: 30% vs. 31% Recurrent: 70% vs. 69% Prior BCG: 26% vs. 28%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Au, 2001[149] RCT Medium	Percent recurrence-free at 5 years: 41% vs. 25% Recurrences: 51% (61/119) vs. 66% (73/111), RR 0.78 (95% CI 0.63 to 0.97) Time to recurrence (median, months): 29 vs. 12 (p=0.005)	Percent recurrence-free at 5 years Multifocal: 35% vs. 19% Unifocal: 50% vs. 32% Ta: 41% vs. 25% T1: 41% vs. 23% Papillary: 41% vs. 24% Recurrent: 37% vs. 24% Grade I/II: 38% vs. 23% No prior intravesical treatment: 30% vs. 27% Prior intravesical treatment: 44% vs. 23% Recurrences Multifocal: 58% (39/67) vs. 70% (44/63) Unifocal: 42% (22/52) vs. 60% (29/48) Ta: 51% (39/76) vs. 67% (50/75) T1: 52% (17/33) vs. 64% (16/25) Papillary: 51%(56/109) vs. 66% (66/100) CIS: 50% (5/10) vs. 64% (7/11) Recurrent: 57% (47/83) vs. 68% (52/77) Primary: 39% (14/36) vs. 62% (21/34) G3: 50% (15/30) vs. 61% (17/28) G1/2: 52% (46/89) vs. 67% (56/83) No prior intravesical treatment: 65% (26/40) vs. 68% (25/37) Prior intravesical treatment: 49% (21/43) vs. 68% (27/40) Time to recurrence (median, months) Multifocal: 16 vs. 7.9 (p=0.008) Unifocal: 44 vs. 17 (p=0.12) Ta: 30 vs. 13 (p=0.01) T1: 13 vs. 7.1 (p=0.29) Papillary: 29 vs. 12 (p=0.008) CIS: 34 vs. 14 (p=0.30) Recurrent: 18 vs. 9.5 (p=0.04) Primary: 34 vs. 14 (p=0.03) G3: 34 vs. 13 (p=0.31)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Au, 2001[149] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Au, 2001[149] RCT Medium	Discontinuation of treatment due to adverse events: 1.8% (2/111) vs. 1.9% (2/106) Dysuria: 33% (37/111) vs. 18% (19/106), RR 1.86 (95% CI 1.15 to 3.02) Cystitis: 23% (26/111) vs. 16% (17/106), RR 1.46 (95% CI 0.84 to 2.53) Urinary frequency: 24% (27/111) vs. 31% (33/106) Urinary urgency: 22% (24/111) vs. 26% (28/106) Hematuria: 26% (29/111) vs. 23% (24/106) Fever: 3.6% (4/111) vs. 4.7% (5/106) Fatigue: 18% (20/111) vs. 19% (20/106) Nausea: 10% (11/111) vs. 8.5% (9/106)		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Bouffioux, 1995[150] RCT Medium	Europe Multicenter 1983-1986	Completely resectable, Ta or T1 (0 or A), papillary transitional cell carcinoma of the bladder (single or multiple, primary or recurrent), previous intravesical treatment with cytotoxic drugs other than mitomycin C allowed if >3 months prior	Another cancer, previous treatment with local or systemic chemotherapy within 3 months, radiation therapy within 12 months, survival of 3 years unlikely, BUN or creatinine >50% above the upper limit or normal, WBC <3,000/mm3, platelet count, <100,000/mm3, untreated UTI	Initial randomization: A. Mitomycin C 30 mg/50 ml saline or doxorubicin 50 mg, 9 instillations starting on day of TURBT (once weekly for 4 weeks, then once monthly for 5 months) B. Mitomycin C 30 mg/50 ml saline or doxorubicin 50 mg, 9 instillations, starting between days 7 and 15 after TURBT (once weekly for 4 weeks, then once monthly for 5 months) Second randomization at 6 months: A: Continued instillations once a month for 6 months, total 15 B: No maintenance

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Bouffioux, 1995[150] RCT Medium	Duration, average: 2.75 to 6.5 years (varied by outcome) Method: Cystoscopy every 3 months during year 1, every 4 months during year 2, every 6 months thereafter	Screened: Not reported Randomized: 965 underwent initial randomization (483 to early treatment, 482 to delayed treatment), 626 underwent second randomization (312 to maintenance and 313 to no maintenance) Postrandomization exclusions: 113 Loss to followup: 18 Analyzed: 834 (417 received mitomycin C, 417 doxorubicin)	Age: <50 8.2%, 50-59 20%, 60-69 34%, 70-79 31%, >80 7.1% Male: 81% Race: NR Smoking status: NR Primary: 44% Recurrent: 56% Ta: 57% T1: 41% CIS: 1.1% G1: 41% G2: 45% G3: 13% Gx: 0.7% Tumor >3 cm: 17% Single tumor: 52%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Bouffioux, 1995[150] RCT Medium	Early vs. delayed treatment Time to first recurrence: 43% (161/374) vs. 49% (187/378) after 2.75 years (p=0.18, log-rank test) Recurrence rate: 0.27 vs. 0.33 (p=0.08) Progression to invasive bladder cancer: 11% (40/374) vs. 10% (38/378) after 6.5 years Distant metastasis: 6% (24/412) vs. 6% (17/412) Second primary: 7% (28/412) vs. 6% (25/412) Mortality: 19% (78/412) vs. 21% (86/412) (p=0.60) Maintenance vs. no maintenance Time to first recurrence: 43% (130/303) vs. 50% (156/314) after 3 years (p=0.20, log-rank test) Recurrence rate: 0.23 vs. 0.28 (p=0.20) Progression to invasive bladder cancer: 9% (26/303) vs. 8% (25/314) Distant metastasis: 4% (12/304) vs. 4% (13/314) Second primary: 5% (15/304) vs. 7% (21/314) (p=0.41) Mortality: 17% (53/304) vs. 20% (63/314)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Bouffioux, 1995[150] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Bouffioux, 1995[150] RCT Medium	Early vs. delayed Chemical cystitis requiring delay or discontinuation of therapy: 3% vs. 0% with mitomycin C, 2.2% vs. 0.5% with doxorubicin Systemic toxicity requiring discontinuation of instillations: 1.8% with mitomycin C, 0.8% with doxorubicin	Not reported	Two parallel trials of mitomycin C and doxorubicin analyzed together

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ersoy, 2013[58] RCT High	Turkey Single site Study years: February 2006 - November 2010	Primary low-risk nonmuscle-invasive bladder cancer (NMIBC). Stage Ta, Grade G1. Solitary tumor; Size < 3 cm.	"Medium or high risk NMIBC"; Muscle-invasive bladder cancer; Suspected bladder perforation.	A: Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.
Flamm, 1990[151] RCT Medium	Austria Single center 1979-1981	Primary or recurrent transitional cell carcinoma of the bladder, otherwise not specified	Previous radiotherapy of the bladder, intravesical therapy within the last 6 months	A: Doxorubicin 50 mg/50 ml saline weekly for 6 weeks, then monthly for 2 years B: Doxorubicin 50 mg/50 ml saline weekly for 6 weeks

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ersoy, 2013[58] RCT High	Duration, median: A vs. B vs. C: 51 vs. 50 vs. 54 months, p = 0.815 Method: Cystoscopy: month 3, month 12, then annually for 5 years.	Screened: NR Randomized: 53 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 49 Per Group Analyzed (A vs. B vs. C): 11 vs. 15 vs. 23	A vs. B vs. C Age, mean: 59.3 vs. 63.5 vs. 61.9 years, p = 0.716 Race: NR Male: 81.8% vs. 86.7% vs. 95.7%, p = 0.395 History of smoking: 63.6% vs. 73.3% vs. 91.3%; p = 0.124 Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 100% vs. 100% Functional Status: NR
Flamm, 1990[151] RCT Medium	Duration: 5 years Method: Cystoscopy every 3 months for 2 years, then every 6 months	Screened: Not reported Randomized: 160 Postrandomization exclusions: Not reported Loss to followup: Unclear Analyzed: 146 (70 vs. 76)	Age (mean): 67 vs. 69 years Male: 64% vs. 63% Race: NR Smoking status: NR Primary: 70% vs. 72% Recurrent: 30% vs. 28% Ta: 49% vs. 51% T1: 51% vs. 49% Concomitant Tis: 8.6% vs. 5.3% G1: 51% vs. 47% G2: 29% vs. 38% G3: 20% vs. 14% Solitary: 44% vs. 51% Tumor weight <5 g: 60% vs. 53%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ersoy, 2013[58] RCT High	A vs. B Recurrence free at 1 year: 100% vs. 86.7%, p = 0.132 Recurrence free at 3 years: 100% vs. 79.4%, p = 0.132 Recurrence free at 5 years: 100% vs. 79.4%, p = 0.173 Mean time to recurrence, months (95% CI): NR vs. 34.8 (28.5-41.1)	NR
Flamm, 1990[151] RCT Medium	Recurrence: 47% (33/70) vs. 42% (32/76), RR 1.1 (95% CI 0.78 to 1.6) Time to first recurrence (months): 16 vs. 13 (p=0.78) Recurrence rate: 1.7 vs. 1.4 per 100 patient-months (p>0.1) Progression: 19% (13/70) vs. 20% (15/76), RR 0.94 (95% CI 0.48 to 1.8) All-cause mortality: 21% (15/70) vs. 24% (18/76), RR 0.90 (95% CI 0.49 to 1.7) Bladder cancer mortality: 13% (9/70) vs. 13% (10/76), RR 0.95 (95% CI 0.41 to 2.2)	Recurrence rate (per 100 patient-months) (p>0.1 in all subgroups) Primary: 1.33 vs. 1.03 Recurrent: 2.85 vs. 2.65 Solitary: 0.67 vs. 0.98 Multiple: 2.77 vs. 2.03 <5 g: 1.62 vs. 1.51 >5 g: 1.98 vs. 1.36 Ta: 1.45 vs. 1.23 T1: 2.03 vs. 1.69

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Ersoy, 2013[58] RCT High	NR	A vs. B vs. C Recurrence free survival according to sex, (p = 0.769): Male, 1-year: 90.9%; 3-years: 85.9%; 5-years: 85.9% Female, 1-year: 100.0%; 3-years: 66.7%; 5-years: NR Mean time to recurrence according to sex, months (95% CI): Male: 53.0 (47.7-58.2) Female: 44.9 (28.6-61.1) Recurrence free survival according to history of smoking (p =0.645): None, 1-year: 100.0%; 3-year: 85.7%; 5-years: 85.7% Present, 1-year: 89.7%; 3-years: 84.2%; 5-years: 84.2% Mean time to recurrence according to history of smoking, months (95% CI): None: 54.9 (45.8-64.1) Present: 52.1 (46.3-57.9)
Flamm, 1990[151] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ersoy, 2013[58] RCT High	NR	NR	
Flamm, 1990[151] RCT Medium	Chemical cystitis: 12.8% vs. 11.8%	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Friedrich, 2007[108] RCT Medium	Germany, Multicenter 1995-2002	Patients with primary transitional cell carcinoma of the bladder or patients with tumor recurrence after TURBT without prior adjuvant therapy were eligible if the histopathologic evaluation of their completely resected tumor revealed an intermediate risk pTaG1 tumor (size >3 cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with T1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	MIBC or concomitant CIS, evidence of lymph node or distant metastasis, or a pT1G3 tumor≥2.5cm.	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations C. MMC 20 md, 6 weekly instillations followed by monthly instillations of MMC 20 mg for 3 years
Giannakopoulos, S, 1998[2] RCT Medium	Greece Number sites: Unclear (authors from 3 centers) Study years: NR	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Stage ≥ T2. Grade G1 or G3 (any stage). CIS; Other concomitant malignancy; Serious systemic disease; Previous intravesical chemotherapy or immunotherapy; TCC of upper urinary tract; Previous systemic chemo/immunotherapy or pelvic radiation therapy	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (IFN-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (IFN-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (IFN-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First installation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Installations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Friedrich, 2007[108] RCT Medium	Duration, median: 2.9 years Method: Cytology and cystoscopy every 3 months in the first 2 years and every 6 months thereafter	Screened: Not reported Randomized: 495 (179 vs 163 vs 153) Postrandomization exclusions: None reported Loss to followup: 11% equally distributed between arms Analyzed: 495 (179 vs 163 vs 153)	Age (median): 68 vs 67 vs 67 Male: 79% vs 80% vs 82% Race: Not reported Smoking status: Not reported Stage/grade: TaG1: 15% vs 12% vs 5% TaG2: 54% vs 45% vs 54% TaG3: 2% vs 3% vs 2% T1G1: 3% vs 3% vs 2% T1G2: 22% vs 31% vs 27% T1G3: 3% vs 6% vs 11%
Giannakopoulos, S, 1998[2] RCT Medium	Duration: 36 months Method: Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter.	Screened: NR Randomized: 89 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 89 Per Group Analyzed (A vs. B vs. C vs. D): 20 vs. 22 vs. 24 vs. 23	A vs. B vs. C vs. D Age, mean: 61.6 vs. 62.1 vs. 60.9 yrs vs. 61.9 yrs; p > 0.10 Race: NR Male: 80.0% vs. 81.8% vs. 79.2% vs. 82.6% ; p > 0.10 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 60.0% vs. 59.1% vs. 62.5% vs. 56.5%; T1: 40.0% vs. 40.9% vs. 37.5% vs. 43.5%; p > 0.10 Grade: All G2 Functional Status: NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Friedrich, 2007[108] RCT Medium	A vs. C Recurrence: 26% (46/179) vs10% (16/153), RR 2.5 (95% CI 1.5 to 4.2) Percent recurrence-free at 2 years: 71% (126/179) vs 88% (135/153) Percent recurrence-free at 3 years:69% (123/179) vs 86% (132/153) (log-rank test, p=0.0006) Recurrence-free interval: Adjusted HR 0.38 (95% CI 0.21 to 0.69) for C vs. A after adjustment for facility, primary/recurrent, stage/grade	A vs. C Percent recurrence-free at 3 years TaG2: 70% vs. 90% (log-rank, p=0.009) T1G2: 74% vs. 81% (log-rank, p=0.29) Primary bladder cancer: 70% vs. 85% (log-rank, p=0.01) Recurrent bladder cancer: 59% vs. 92% (log-rank, p=0.005)
Giannakopoulos, S, 1998[2] RCT Medium	B vs. C vs. D Recurrence: 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): 21.4 vs. 26.1 vs. 30.0; B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: 1.19 vs. 0.88 vs. 0.63; B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS	B vs. C vs. D Simple recurrence rate according to stage: Ta: 50.0% (4/8) vs. 57.1% (4/7) vs. 40.0% (2/5); For all comparisons between groups, p > 0.10. T1: 50.0% (4/8) vs. 42.9% (3/7) vs. 60.0% (3/5); For all comparisons between groups, p > 0.10. Recurrence-free survival time according to stage, Mean months (SD): Ta: 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); B vs. C, p = 0.05, B vs. D, p < 0.001; C vs. D, p = NS. T1: 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); B vs. C, p = 0.048, B vs. D, p < 0.001; C vs. D, p < 0.01. Recurrence rate per 100 patient-months according to stage: Ta: 0.96 vs. 0.78 vs. 0.44; Differences between B, C, and D, p = NS. T1: 1.55 vs. 1.05 vs. 0.8; Results "similar" to stage Ta, no p=values reported.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Friedrich, 2007[108] RCT Medium		
Giannakopoulos, S, 1998[2] RCT Medium	B vs. C vs. D Simple recurrence rate: Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): B vs. C, p = 0.02, B vs. D, p < 0.01; C vs. D, p = NS. Recurrence rate per 100 patient-months: B vs. C, p = "significant", B vs. D, p = "significant"; C vs. D, p = 0.026. Progression: B vs. C, p = NS, B vs. D, p = NS; C vs. D, p = NS.	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Friedrich, 2007[108] RCT Medium	Withdrawals due to AE: 0 vs 3 vs 8 Dysuria: 12% vs 20% Hematuria: 1% vs 9% Fever: 2% vs 2%	Fa. Medac GmbH	
Giannakopoulos, S, 1998[2] RCT Medium	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups not reported) developed fevers and were found to have urinary tract infections.	NR	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gruenwald, 1997[152] RCT Medium	Israel Single center 1992-1994	Multifocal (≥3) tumors of any stage or grade, ≥3 recurrences within 12 months (regardless of stage), concomitant Tis, stage T1, or grade G3	Not reported	A: Pasteur strain BCG 120 mg/50 ml saline (begun within 1 month after TURBT, once weekly for 6 weeks) B: Pasteur strain BCG 120 mg/50 ml saline (begun within 1 month after TURBT, once weekly for 12 weeks)
Hendricksen, 2008[153] RCT Medium	the Netherlands Multicenter 1998-2004	≤85 years of age, solitary T1 tumor, or multiple primary or recurrent T1 or Ta G1-G3 urothelial cell carcinoma of the bladder in whom complete TURBT was possible	Prior epirubicin therapy (other intravesical therapy allowed), intravesical therapy within 6 months, solitary Ta tumor, CIS, or tumors ≥2, concurrent malignancy, history of other malignancy within 5 years, uncontrollable UTI, previous systematic cancer therapy or radiotherapy, urothelial cell carcinoma in prostatic urethra or upper urinary tract, pregnant or lactating, immunodeficiency, hypersensitivity to anthracyclines	A. Epirubicin 50 mg/50 ml saline, 9 instillations over 6 months (once weekly for 4 weeks started within 2 weeks of TURBT, then once monthly for 5 months) B. Epirubicin 50 mg/50 ml saline, 10 instillations over 6 months (within 48 hours of TURBT, once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months) C: Epirubicin 50 mg/50 ml saline, 11 instillations over 12 months (once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months, once every three months for 6 months)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gruenwald, 1997[152] RCT Medium	Duration, median: 29 months Method: Cystoscopy and cytology every 3 months during year 1, every 6 months during year 2	Screened: Not reported Randomized: 75 Postrandomization exclusions: 5 (2 vs. 3) Loss to followup: None reported Analyzed: 70 (40 vs. 30)	Age (mean): 68 vs. 69 years Male: 88% vs. 90% Race: Not reported Smoking status: Not reported Recurrences in last 12 months: 25% vs. 40% Ta: 30% vs. 30% T1: 70% vs. 70% Tis: 10% vs. 10% G1: 2.5% vs. 6.6% G2: 55% vs. 63% G3: 42% vs. 30% Tumor size: Not reported Single: Not reported
Hendricksen, 2008[153] RCT Medium	Duration, median (A and B, not reported for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: Not reported Randomized: 1000 Postrandomization exclusions: 269 (101 vs. 91 vs. 77) Loss to followup: Not reported Analyzed: 731 (239 vs. 238 vs. 254)	Age (mean): 67 years (overall) Male: 80% (overall) Race: Not reported Smoking status: Not reported Ta: 79% vs. 82% vs. 74% T1: 21% vs. 18% vs. 26% G1: 45% vs. 42% vs. 38% G2: 45% vs. 46% vs. 49% G3: 8.8% vs. 11% vs. 12% Single tumor: 20% vs. 18% vs. 22% Primary: 48% vs. 46% vs. 52% Recurrent: 52% vs. 54% vs. 48% Prior intravesical therapy: 17% vs. 15% vs. 12%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Gruenwald, 1997[152] RCT Medium	Bladder cancer and all-cause mortality: 5.0% (2/40) vs. 3.3% (1/30), RR 1.5 (95% CI 0.14 to 16) Percent recurrence-free: 55% (22/40) vs. 70% (21/30) (p>0.05); adjusted OR 2.17 for B vs. A (95% CI 0.9 to 5.22) (adjusted for stage and number of recurrences) Time to recurrence: 12.3 vs. 12.9 months Recurrence: 20% (8/40) vs. 13% (4/30) at 1 year, RR 1.5 (95% CI 0.50 to 4.5); 45% (18/40) vs. 30% (9/30) at 2 years, RR 1.5 (95% CI 0.79 to 2.86) Progression: 5.0% (2/40) vs. 10% (3/30), RR 0.50 (95% CI 0.09 to 2.81) Radical cystectomy: 5.0% (2/40) vs. 6.7% (2/30), RR 0.75 (95% CI 0.11 to 5.0)	Greater difference in risk estimates favoring 12 week course in patients with higher risk cancer, based on stage and number of recurrences in the year before treatment (data not reported)
Hendricksen, 2008[153] RCT Medium	Percent recurrence-free at 5 years: 44.4% vs. 42.7% vs. 45.0% (p=0.712, log-rank) % progression-free at 5 years: 90.0% vs. 87.7% vs, 88.2% (p=0.593, log-rank)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Gruenwald, 1997[152] RCT Medium		
Hendricksen, 2008[153] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gruenwald, 1997[152] RCT Medium	Dysuria or frequency: 30% (12/40) vs. 40% (12/30) Hemorrhagic cystitis: 7.5% (3/40) vs. 13% (4/30) Fever (mild): 22% (9/40) vs. 30% (9/30) Severe side effects: 2.5% (1/40) vs. 6.7% (2/30)	Not reported	Terminated early due to unavailability of Pasteru strain BCG
Hendricksen, 2008[153] RCT Medium	Therapy stopped or delayed due to side effects: 15% (39/266) vs. 22% (62/286) vs. 22% (61/277) Chemical cystitis: 32% (84/266) vs. 33% (95/286) vs. 24% (66/277) Hematuria: 13% (36/266) vs. 19% (54/286) vs. 11% (30/277) Systemic side effects: 13% (35/266) vs. 14% (40/286) vs. 14% (37/277)	Pfizer, the Netherlands	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hinotsu, 2011[112] RCT Medium	Japan Multicenter 2004-2006	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or with recurrence diagnosed within 12 months from previous TURBT for NMIBC	History of BCG instillation or an anthracycline anti-tumor drug within the 12 months following the day on which the TURBT was performed (1 course of BC more than 12 months earlier permitted and MMC therapy allowed after a washout period of at least 4 weeks); stage T2 or higher; IV/IA anticancer/ chemotherapy, radiation	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 ml saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 ml saline weekly for 6 weeks C. Epirubicin 40 mg in 40 ml saline twice at 1-week interval and then 7 times at 2-week intervals
Hoeltl, 1991[154] RCT Medium	Austria Single center Study years not reported (publication date 1991)	Primary G1 or G2 papillary transitional cell carcinoma of bladder stages Ta, T1, or TIS or recurrent G1/Ta or T1 bladder cancer; Karnofsky performance status ≥50%	Prior intravesical or systemic chemotherapy or immunotherapy, other cancers, pelvic irradiation within 3 months, Cr >2.5, bilirubin >1.12, WBC <2500, platelet count <100,000	A: Interferon alfa-2b 100 x 10^6 IU (100 MU)/30 ml sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) B: Interferon alfa-2b 10 x 10^6 IU (10 MU)/30 ml sterile water (starting within 36 hours of TURBT, once weekly for 10 weeks, then once monthly for 1 year total of therapy) C: Ethoglucid 1.13 g/100 ml sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Hinotsu, 2011[112] RCT Medium	Duration, median: 2 years Method: Cystoscopy and cytology every 3 months for 3 years then every 6 months	Screened: Not reported Randomized: 116 Postrandomization exclusions: 5 in BCG maintenance group as had no maintenance instillations Loss to followup: None reported Analyzed: 110 (41 vs 42 vs 32)	Age ≤ 64: 17 vs 22 vs 11 Age > 64: 24 vs 20 vs 21 Male: 80% vs 95% vs 97% Race: Not reported Smoking: Not reported Stage: pTa: 71% vs 69% vs 75% pT1: 29% vs 31% vs 26% Grade 1: 12% vs 24% vs 13% Grade 2: 71% vs 57% vs 68% Grade 3: 17% vs 19% vs 23%
Hoeltl, 1991[154] RCT Medium	Duration, mean: 36.5 months Method: Cystoscopy and urine cytology every 3 months for 1 year, then every 6 months	Screened: Not reported Randomized: 44 Postrandomization exclusions: 10 Loss to followup: Not reported Analyzed: 34 (14 vs. 14 vs. 16)	Age (mean): 68 vs. 68 vs. 73 years Male: 55% vs. 60% vs. 77% Race: Not reported Smoking status: Not reported Ta: 0% vs. 7.7% vs. 10% T1: 91% vs. 85% vs. 80% Tis: 9.1% vs. 7.7% vs. 10% G1: 73% Vs. 77% vs. 70% G2: 18% vs. 15% vs. 20% G3: 9.1% vs. 7.7% vs. 10% Single tumor: 36% vs. 54% vs. 50% Primary: 36% Vs. 46% vs. 50% Recurrent: 64% vs. 54% vs. 50%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Hinotsu, 2011[112] RCT Medium	A vs. B Recurrence: 12% (5/41) vs 33% (14/42), RR 0.37 (95% CI 0.14 to 0.92) Progression at time of recurrence: 0% (0/41) vs. 7.1% (3/42), RR 0.15 (0.01 to 2.7) Recurrence-free survival: 85% vs. 65% (p=0.02)	
Hoeltl, 1991[154] RCT Medium	A vs. B Recurrence rate: 2.76 vs. 4.4 per 100 months Percent recurrence-free: 54.5% (6/11) vs. 46.2% (6/13), RR 1.2 (95% CI 0.53 to 2.62) Time to recurrence (mean, months): 22.4 vs. 22.2 Progression (recurrence of G2 or G3 cancer, ≥T2, or metastatic): 36.4% (4/11) vs. 7.7% (1/13), RR 4.7 (95% CI 0.62 to 36)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Hinotsu, 2011[112] RCT Medium		
Hoeltl, 1991[154] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hinotsu, 2011[112] RCT Medium	A vs. B Urinary frequency: 93% (39/42) vs. 71% (30/42), RR 1.3 (95% CI 1.1 to 1.6) Dysuria: 93% (39/42) vs 69% (29/42), RR 1.3 (95% CI 1.1 to 1.7) Hematuria: 93% (39/42) vs 71% (30/42), RR 1.3 (95 %CI 1.1 to 1.6) Fever: 43% (18/42) vs 26% (11/42), RR 1.6 (95% CI 0.88 to 3.0)	Nippon Kayaku Co. Ltd. (current Japanese license holder for the BCG Connaught strain)	
Hoeltl, 1991[154] RCT Medium	A vs. B Local toxicity (chemocysstitis, dysuria): 0% (0/11) vs. 0% (0/13) Systemic side effects: None observed	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Huland, 1990[114] RCT Medium	Germany (Hamburg) Multicenter Study years: March 1983 - June 1985	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	"Prophylactic installation not possible because of patient age, immobility or lack of cooperation". Grade 0 tumor.	A: Mitomycin C, 20 mg/20 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: Mitomycin C, 20 mg/20 ml. Total 42 installations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: Mitomycin C, 20 mg/20 ml. Total 20 installations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Installations started 4 to 6 weeks after discharge from hospital.
Irie, 2003[155] NRCT Low	Japan Single center 1996-2001	Superficial papillary bladder cancer, no prior BCG or chemotherapeutic agents, stage Ta or T1	Not reported	A. BCG (Tokyo 172 strain) 40 mg/40 ml saline, 6 instillations weekly starting 7-50 days after TURBT B: BCG (Tokyo 172 strain) 80 mg/40 ml saline, 6 instillations weekly starting 7-50 days after TURBT

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Huland, 1990[114] RCT Medium	Duration, mean: A vs. B vs. C vs. D: 26.7 vs. 27.4 vs. 26.7 vs. 30.2 months Method: Cystoscopy every 3 months.	Screened: 597 Randomized: 477 Postrandomization exclusions: 29 Lost to followup: NR Total Analyzed: 419 Per Group Analyzed: 209 vs. 96 vs. 75 vs. 39	A vs. B vs. C vs. D Age, mean (men/women): 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs .68.0/58.3 Race: NR Male: 82.3% vs. 77.1% vs. 77.3% vs. 74.4% Smoking status: NR Recurrent bladder cancer: 32.1% vs. 25.0% vs. 25.3% vs. 43.6% Stage: Ta: 73.7% vs. 78.1% vs. 76.0% vs. 59.0%; T1: 23.0% vs. 19.8% vs. 21.3% vs. 33.3%; Tis: 3.3% vs. 2.1% vs. 29.3% vs. 7.7% Grade: G1: 47.4% vs. 58.3% vs. 52.0% vs. 43.6%; G2: 47.7% vs. 35.4% vs. 37.3% vs. 38.5%; G3: 1.9% vs. 4.2% vs. 8.0% vs. 10.3%; CIS: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% Functional Status: NR
Irie, 2003[155] NRCT Low	Duration, mean: 27.5 months in 40 mg group and 20 months in 80 mg group Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months	Screened: Not reported Randomized: Not reported Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 80 (41 vs. 39)	Age (mean): 62 vs. 62 years Male: 80% vs. 90% Race: Not reported Smoking status: Not reported Ta: 22% vs. 31% T1: 78% vs. 69% Concurrent CIS: 0% vs. 7.7% G1: 56% vs. 41% G2: 31% vs. 44% G3: 4.9% vs. 15% Primary: 93% vs. 84% Recurrent: 7% vs. 16% Unifocal: 63% vs. 64%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Huland, 1990[114] RCT Medium	A vs. B vs. C Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75)	A vs. B vs. C Primary bladder cancer (n = 288) Ta: 9.6% (10/104) vs. 6% (3/50) vs. 15% (6/40) T1: 14.7% (5/34) vs. 0% (0/17) vs. 13.3% (2/15) CIS: 66.7% (2/3) vs. 0% (0/2) vs. 0% (0/1) G1: 7.9% (5/63) vs. 7.5% (3/40) vs. 14.3& (4/28) G2: 12.7% (9/71) vs. 0% (0/24) vs. 13.0% (3/23) G3: 9% (1/9) vs. 0% (0/3) vs. 0% (0/5) Recurrent bladder cancer (n = 131) Ta: 28.0% (14/50) vs. 20% (5/25) vs. 29.4% (5/17) vs. 10% (1/10) T1: 7.1% (1/14) vs. 50% (1/2) vs. 29.4% (5/17) vs. 10% (1/10) CIS: 0% (0/4) vs. 0% (0/0) vs. 0% (0/1) vs. 100% (1/1) G1: 13.9% (5/36) vs. 25% (4/16) vs 9.1% (1/11) vs. 0% (0/8) G2: 35.7% (10/28) vs. 20% (2/10) vs. 80% (4/5) vs. 14.3% (1/7) G3: 0% (0/2) vs. 0% (0/3) vs. 0% (0/3) vs 100% (2/2)
Irie, 2003[155] NRCT Low	Recurrence: 28% (11/40) vs. 16% (5/31), RR 1.71 (95% CI 0.66 to 4.40) Progression: 5.0% (2/40) vs. 6.4% (2/31), RR 0.78 (95% CI 0.12 to 5.20)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Huland, 1990[114] RCT Medium	A vs. B vs. C Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75)	NR
Irie, 2003[155] NRCT Low		No statistically significant effects of sex or age on recurrence in multivariate analysis

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Huland, 1990[114] RCT Medium	A vs. B vs. C Chemical cystitis: 25% vs. 12% vs. 18% Allergy: 2% vs. 2% vs. 1% Other: 6% vs. 4% vs. 10% Total: 33% vs. 18% vs. 29%	NR	
Irie, 2003[155] NRCT Low	Discontinuation of treatment due to adverse effects: 2% (1/40) vs. 21% (8/39), RR 0.12 (95% CI 0.02 to 0.93) Fever: 6% (2/35) vs. 13% (5/39), RR 0.45 (95% CI 0.09 to 2.15) Bladder irritability: 27% (10/37) vs. 53% (20/38), RR 0.51 (95% CI 0.28 to 0.94) Gross hematuria: 9% (3/34) vs. 23% (7/30), RR 0.38 (95% CI 0.11 to 1.33)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Koga, 2004[156] RCT Medium	Japan Multicenter 1993-1995	New, untreated transitional cell carcinoma of the bladder, Ta or T1 disease, no residual tumor based on cystoscopy and cytology	Other active neoplasms or serious complications, urothelial carcinoma orf the renal pelvis or ureter	A: Epirubicin 30 mg/30 ml saline 19 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 12 weeks, then once a month for 9 months) B: Epirubicin 30 mg/30 ml saline 9 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 10 weeks)
Koontz, 1981[69] (treatment) RCT Medium	USA Multicenter 1974-1977	Incompletely resected NMIBC (single or multiple) or Tis or carcinoma on random biopsy	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 ml distilled water (once weekly for 4 weeks, repeated after 4 weeks) B: Thiotepa 60 mg/60 ml distilled water (once weekly for 4 weeks, repeated after 4 weeks)
Koontz, 1981[69] (prophylaxis) RCT Medium	USA Multicenter 1974-1977	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 ml distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 ml distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Koga, 2004[156] RCT Medium	Duration, median: 30.6 months Method: Cytology every month, cystoscopy every 3 months for 2 years, then every 6 months	Screened: Not reported Randomized: 171 Postrandomization exclusions: 21 Loss to followup: 22 (14 vs. 8) Analyzed: 150 (77 vs. 73)	Age (mean): 66 vs. 64 years Male: 71% vs. 75% Race: Not reported Smoking status: Not reported Primary: All Ta: 79% vs. 85% T1: 21% vs. 15% G1: 21% vs. 29% G2: 65% vs. 63% G3: 14% vs. 8.2% Unifocal: 61% vs. 60% >3 cm: 5.2% vs. 8.2%
Koontz, 1981[69] (treatment) RCT Medium	Duration: 4 weeks after 2 4-week treatment courses Method: Cystoscopy at 4 weeks after fourth instillation and 4 weeks after eight instillation	Screened: Not reported Randomized: 101 Postrandomization exclusions: 6 Loss to followup: Not reported Analyzed: 95 (50 vs. 45)	Age (median): 65 years Male: 82% Race: Not reported Smoking status: Not reported Primary: Not reported Ta: 46% T1: 24% Tis: 21% G1: 33% G2: 35% G3: 28% Unifocal: 19% ≥3 cm: 25%
Koontz, 1981[69] (prophylaxis) RCT Medium	Duration, median: 15 months Method: Cystoscopy every 3 months	Screened: Not reported Randomized: 95 Postrandomization exclusions: 2 Loss to followup: Not reported Analyzed: 93 (23 vs. 23. vs. 47)	Age (median): 65 years Male: 88% Race: Not reported Smoking status: Not reported Primary: Unclear Stage: Not reported Grade: Not reported Multifocal: Unclear Tumor size: Not reported

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Koga, 2004[156] RCT Medium	Percent recurrence-free at 3 years: 85.2% vs. 63.9% (p=0.005) Recurrence: 13.0% (10/77) vs. 31.5% (23/77); unadjusted HR 0.39 (0.18 to 0.82), adjusted HR 0.36 (0.17 to 0.78) (adjusted for multiplicity and tumor stage)	
Koontz, 1981[69] (treatment) RCT Medium	Success (slight or moderate reduction of tumor, or complete remission): 70% (35/50) vs. 58% (26/45), RR 1.21, 95% CI 0.89 to 1.65 after first course; 48% (24/50) vs. 47% (21/45), RR 1.03, 95% CI 0.67 to 1.57) after second course	
Koontz, 1981[69] (prophylaxis) RCT Medium	Percent recurrence-free at 12 months: 63% vs. 69% vs. 40% (p=0.02 for A or B vs. C)	A or B vs. C Percent recurrence-free at 12 months Cytology positive: 56% vs. 40% Cytology negative: 69% vs. 40%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Koga, 2004[156] RCT Medium		
Koontz, 1981[69] (treatment) RCT Medium		
Koontz, 1981[69] (prophylaxis) RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Koga, 2004[156] RCT Medium	Severe local toxicity: 5.2% (4/77) vs. 8.2% (6/73), RR 0.63 (95% CI 0.19 to 2.15) Discontinuation of instillation due to pain: 1.3% (1/77) vs. 0% (0/73) Systemic toxicity (fatigue, low grade fever): 0% (0/77) vs. 2.7% (2/73) Microhematuria (mild, moderate, severe): 30% (23/77) vs. 16% (12/73) Dysuria (mild, moderate, severe): 38% (29/77) vs. 37% (27/73) Frequency (mild, moderate, severe): 32% (25/77) vs. 30% (22/73)	Not reported	
Koontz, 1981[69] (treatment) RCT Medium	Leukopenia (WBC <3000): 2.0% (1/50) vs. 13% (6/45), RR 0.15 (95% CI 0.02 to 1.20) Thrombocytopenia (platelets <100,000): 6.0% (3/50) vs. 0% (0/45) UTI: 2.0% (1/50) vs. 2.2% (1/45)	Not reported	
Koontz, 1981[69] (prophylaxis) RCT Medium	Leukopenia (WBC <3000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) Thrombocytopenia (platelets <100,000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) UTI: 0% (0/23) vs. 17% (4/23) vs. 0% (0/47)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Kuroda, 2004[157] RCT Medium	Japan Multicenter 1994-1996	Primary or recurrent superficial transitional cell carcinoma of the bladder (Ta or T1, G1 or G2)	CIS or G3 tumors, primary and solitary bladder cancer, other severe illness	A. Epirubicin 20 mg/40 ml saline, 17 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 8 months) B: Epirubicin 30 mg/40 ml saline, 12 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 3 months) C: Epirubicin 40 mg/40 ml saline, 9 instillations over 4 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Kuroda, 2004[157] RCT Medium	Duration, median: 3.5 years Method: Cystoscopy every 3 months	Screened: Not reported Randomized: 622 Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 614 (205 vs. 204 vs. 205)	Age 50-59: 18% vs. 19% vs. 19% Age 60-69: 36% vs. 40% vs. 33% Age ≥70: 41% vs. 35% vs. 40% Male: 78% vs. 78% vs. 83% Race: Not reported Smoking status: Not reported Ta: 51% vs. 49% vs. 448% T1: 48% vs. 48% vs. 47% G1: 35% vs. 34% vs. 35% G2: 65% vs. 63% vs. 60% Primary: 54% vs. 54% vs. 55% Recurrent: 46% vs. 46% vs. 45% >3 cm: 12% vs. 8.3% vs. 5.9% Unifocal: 17% vs. 18% vs. 19%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Kuroda, 2004[157] RCT Medium	Percent recurrence-free at 1 year: 67% vs. 73% vs. 74% Percent recurrence-free at 2 years: 49% vs. 55% vs. 60% Percent recurrence-free at 4 years: 36% vs. 46% vs. 44% Time to recurrence (median, days): 688 vs. 1007 vs. 1186 (p=0.04 for dose-response) Mortality: 5.4% (11/205) vs. 6.4% (13/204) vs. 8.8% (18/205); RR 0.84 (95% CI 0.39 to 1.8) for A vs. B, RR 0.61 (95% CI 0.30 to 1.3) for A vs. C, and RR 0.73 (95% CI 0.37 to 1.4) for B vs. C Bladder cancer mortality: 1.5% (3/205) vs. 1.5% (3/204) vs. 2.4% (5/205), RR 1.0 (95% CI 0.20 to 4.9) for A vs. B, 0.60 (95% CI 0.15 to 2.5) for A vs. C, and RR 0.60 (95% CI 0.15 to 2.5) for B vs. C	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Kuroda, 2004[157] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kuroda, 2004[157] RCT Medium	Frequency (mild, moderate, severe): 22% vs. 35% vs. 29% Pain on urination (mild, moderate, severe): 21% vs. 32% Vs. 30% Dysuria (mild, moderate, severe): 12% vs. 17% vs. 15% Hematuria (mild, moderate, severe): 19% vs. 25% vs. 20%	Pfizer Inc. Oncology Japan	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Liu, 2006[120] RCT Medium	China Number sites: NR Study years: May 1997 - February 1998	Superficial bladder carcinoma (primary or recurrent). Stages Ta or T1; Grade G1 or G2	No recurrence within 1 year prior to enrollment. CIS; muscle-invasive disease (stage pT2 or greater); age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Epirubicin, 80 mg (in 40 ml normal saline). Single intravesical installation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months. C: Mitomycin C, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Liu, 2006[120] RCT Medium	Duration: All patients followed-up for 5 years until June 2003. Method: Cystoscopy and urinary cytology every 3 months X 2 years, then every 6 months X 3 years.	Screened: NR Randomized: 47 (16 vs. 15 vs. 16) Postrandomization exclusions: None Lost to followup: None Total Analyzed: 44 (14 vs. 15 vs. 15)	A vs. B vs C Age (overall mean): 62.2 years Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer, overall: 23.4% Stage and Grade: TaG1: 6.3% vs. 0% vs. 0%; TaG2: 6.3% vs. 6.6% vs. 6.3%; T1G1: 12.5% vs. 26.7% vs. 12.5%; T1G2: 75.0% vs. 66.7% vs. 81.3% Functional Status: NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Liu, 2006[120] RCT Medium	A vs. B Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15), RR 1.15 (95% CI 0.91 to 1.44) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15), RR 1.07 (95% CI 0.77 to 1.49) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15), RR 0.89 (95% CI 0.59 to 1.35) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15), RR 0.96 (95% CI 0.57 to 1.64) Mean interval to recurrence, months: 8 vs. 4 vs. 5 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15), RR 1.07 (95% CI 0.39 to 2.92)	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Liu, 2006[120] RCT Medium		NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Liu, 2006[120] RCT Medium	A vs. B Any side effect: 13.6% vs. 53.3% Dysuria or urinary frequency/urgency: 6.3% (1/16) vs. 13.3% (2/15) Stricture of urethra: 0% (0/16) vs. 6.7% (1/15) No systemic adverse events	Pharmacia Ltd.	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Malmström, 2002[124] RCT Medium	Europe (multinational) Multicenter Study years: NR	Histologically confirmed transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Multiple tumors only. Stages Ta or T1; Grade G1 or G2. Karnofsky performance status > 70%; No other malignancy within 5 years of the study, except nonmelanoma skin cancer; Age ≥ 18 years; Not pregnant and on appropriate birth control.	Previous exposure to any interferon or mitomycin-C; Pelvic radiation or treatment with any cytotoxic, immunological or chemotherapeutic agent for benign conditions within 5 years of the study; Abnormal hepatic, renal or bone marrow function, or coagulation disorder; Serious infection or genitourinary surgery within 1 month of study; Bladder capacity < 150 mL and/or bladder obstruction with residual urine volume > 100 mL after spontaneous voiding; Chronic UTI; Previous exposure to any experimental drug within 4 weeks; Any significant medical or psychiatric illness preventing informed consent or following study procedures; History of TCC of upper tract and/or disease limited to prostatic urethra.	A: Interferon-α, 30 MU (in 30 ml sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First installation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks. B: Interferon-α, 50 MU (in 30 ml sterile water). Same procedure as A. C: Interferon-α, 80 MU (in 30 ml sterile water). Same procedure as A. D: Mitomycin-C, 40 mg (in 40 ml sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First installation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Malmström, 2002[124] RCT Medium	Duration: Method: followup at 9 weeks and 13 weeks for all treatment groups and at 9 weeks only for control group. Cystoscopy at week 9 for both groups.	Screened: NR Randomized: 115 (29 vs. 28 vs. 29 vs. 29) Postrandomization exclusions: 1 Lost to followup: None Total Analyzed: 110 (27 vs. 27 vs. 27 vs. 29)	A vs. B vs. C vs. D Age, % ≥ 70 years: 17% vs. 46% vs. 21% vs. 45% Race: All Caucasian, except one Asian (male) and one Arab (male), groups not reported Male: 86% vs. 79% vs. 90% vs. 86% Smoking status: NR Recurrent bladder cancer: NR Stage/Grade: TaG1: 41% vs. 29% vs. 31% vs. 21%; TaG2: 38% vs. 43% vs. 52% vs. 48%; T1G1: 3% vs. 7% vs. 7% vs. 10% ; T1G2: 14% vs. 21% vs. 10% vs. 21% Functional Status: Normal activity: 79% vs. 82% vs. 76% vs. 83%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Malmström, 2002[124] RCT Medium	A vs. B vs. C Complete response (macroscopic disappearance of marker lesion): 19% (5/27) vs. 30% (8/27) vs. 26% (7/27) at 9 weeks; 19% (5/27) vs. 33% (9/27) vs. 41% (11/27) at 13 weeks (p>0.05 for all comparisons)	Not reported

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Malmström, 2002[124] RCT Medium	NA	NA

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Malmström, 2002[124] RCT Medium	A vs. B vs. C vs. D Adverse events reported: 37% (10/27) vs. 37% (10/27) vs. 48% (13/27) vs. 55% (16/29)* Adverse events with frequency ≥ 10%, reported by treatment group: A: None B: Fever (11%); Pain (11%) C: Fever (11%); Pain (15%); Micturition frequency (11%) D: Pain (10%); Dysuria (10%); Hematuria (14%); Micturition disorder (14%); Micturition frequency (28%); UTI (10%) * Reported as "55% (26/29)"; error presumed to be with number of events.	Schering-Plough	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Martinez-Pineiro, 2002[158] RCT Medium	Spain Multicenter 1991-1992	Primary or r4ecurrent TaG2/3 or T1G1-3 bladder cancer with or without CIS; primary Tis; recurrent TaG1 cancers	Previous BCG, severe infection or active tuberculosis, untreatable urinary infection, concomitant urothelial tumor, reduced bladder capacity to <200 ml, elevated Cr, bilirubin and hepatic enzymes >2 times upper limit of normal, expected survival <2 years, other malignancy	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)
Martinez-Pineiro, 2005[159] RCT Medium	Spain Multicenter 1995-1999	T1G3 and Tis bladder cancer	Not reported	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Martinez-Pineiro, 2002[158] RCT Medium	Duration, median: 69 months Method: NR	Screened: Not reported Randomized: 500 (252 vs. 248) Postrandomization exclusions: None reported Loss to followup: Not reported Analyzed: 499 (252 vs. 247)	Age (mean): 64 vs. 63 years Male: 89% vs. 91% Race: Not reported Smoking status: Not reported Primary: 61% vs. 62% Recurrent: 39% vs. 38% Solitary: 56% vs. 57% >3 cm: 18% vs. 19% Ta: 24% vs. 27% T1: 67% vs. 66% Tis primary: 3.2% vs. 2.0% Tis Ta: 0.8% vs. 1.2% Tis T1: 5.1% vs. 3.2% G1: 17% vs. 18% G2: 60% vs. 67% G3: 24% vs. 15% High-risk (T1G3, Tis, ≥2 relapses, ≥3 lesions, or ≥3 cm): 75% vs. 71%
Martinez-Pineiro, 2005[159] RCT Medium	Duration, median: 61 months Method: NR	Screened: Not reported Randomized: 155 (81 vs. 73) Postrandomization exclusions: None reported Loss to followup: 12 (6 vs. 6) Analyzed: 155	Age (mean): 66 vs. 68 years Male: 94% vs. 90% Race: Not reported Smoking status: Not reported Primary: 70% vs. 70% Recurrent: 30% vs. 30% Solitary: 46% vs. 48% >3 cm: 18% vs. 19% T1G3: 56% vs. 60% Tis primary: 18% vs. 11% TisTaG3: 6.1% Vs. 5.1% TisT1G3: 20% vs. 23%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Martinez-Pineiro, 2002[158] RCT Medium	Recurrence: 28% (71/252) vs. 31% (76/247), RR 0.92 (95% CI 0.70 to 1.20) Disease-free interval (B vs. A): HR 1.09 (95% CI 0.79 to 1.51) Progression: 12% (29/252) vs. 13% (33/247), RR 0.86 (95% CI 0.54 to 1.37) Progression-free survival (B vs. A): HR 1.17 (95% CI 0.71 to 1.93) All-cause mortality: 20% (51/252) vs. 22% (55/247), RR 0.93 (95% CI 0.66 to 1.31) Survival time (B vs. A): HR 1.08 (95% CI 0.74 to 1.58) Bladder cancer mortality: 7.9% (20/252) vs. 7.3% (18/247), RR 1.09 (95% CI 0.59 to 2.01) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94) Cystectomy: 4.8% (12/252) vs. 6.1% (15/247), RR 0.78 (95% CI 0.37 to 1.64)	Recurrent High-risk tumors: 30% (56/190) vs. 37% (65/177), RR 0.80 (95% CI 0.60 to 1.08) Progression High-risk tumors: 15% (28/190) vs. 16% (29/177), RR 0.90 (95% CI 0.56 to 1.45) ≥3 tumors: standard dose superior (p=0.04)
Martinez-Pineiro, 2005[159] RCT Medium	Recurrence: 39% (32/82) vs. 45% (33/73), RR 0.86 (95% CI 0.60 to 1.25) Disease-free interval (B vs. A): HR 1.23 (95% CI 0.75 to 2.00) Progression: 24% (20/82) vs. 26% (19/73), RR 0.94 (95% CI 0.54 to 1.61) Progression-free survival (B vs. A): HR 1.08 (95% CI 0.58 to 2.03) All-cause mortality: 29% (24/82) vs. 29% (21/73), RR 1.01 (95% CI 0.62 to 1.67) Bladder cancer mortality: 12% (10/82) vs. 15% (11/73), RR 0.81 (95% CI 0.36 to 1.79) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94) Cystectomy: 8.4% (7/82) vs. 9.5% (7/73), RR 0.89 (95% CI 0.33 to 2.42)	No effect of primary vs. recurrent, single or multiple, small or large, or T category on efficacy of doses for survival

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Martinez-Pineiro, 2002[158] RCT Medium		
Martinez-Pineiro, 2005[159] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Martinez-Pineiro, 2002[158] RCT Medium	Local side effects: 67% (168/252) vs. 55% (135/247), RR 1.22 (95% CI 1.06 to 1.41) Severe (grade 3 or 4) local side effects: 18% (44/252) vs. 6.5% (16/247), RR 2.70 (95% CI 1.56 to 4.65) Systemic side effects: 32% (80/252) vs. 15% (38/247), RR 2.06 (95% CI 1.46 to 2.91) Severe systemic side effects: 3.6% (9/252) vs. 4.4% (11/247), RR 0.80 (95% CI 0.34 to 1.90) Withdrawal due to side effects: 9.1% (23/252) vs. 4.0% (10/247), RR 2.25 (95% CI 1.10 to 4.64)	Not reported	
Martinez-Pineiro, 2005[159] RCT Medium	Local side effects: 70% (57/82) vs. 48% (35/72), RR 1.43 (95% CI 1.08 to 1.89) Severe (grade 3 or 4) local side effects: 20% (16/82) vs. 11% (8/73), RR 1.78 (95% CI 0.81 to 3.92) Systemic side effects: 16% (13/82) vs. 5.5% (4/73), RR 2.89 (95% CI 0.99 to 8.48) Severe systemic side effects: 0% (0/82) vs. 1.4% (1/73), RR 0.30 (95% CI 0.01 to 7.18) Withdrawal due to side effects: 12.2% (10/83) vs. 9.6% (7/73), RR 1.26 (95% CI 0.50 to 3.13)	INIBSA	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Masters, 1999[160] RCT Medium	UK Multicenter 1991-1993	Primary or recurrent Ta or T1 bladder cancer	Previous malignancy, pelvic radiotherapy, WHO performance status >2, UTI	A: Epirubicin 50 mg/50 ml saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) B: Epirubicin 100 mg/50 ml saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) First 102 patients had a marker tumor left after initial TURBT (0.5 cm)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Masters, 1999[160] RCT Medium	Duration: 834 vs. 774 days Method: Cystoscopy every 3 months	Screened: Not reported Randomized: 126 Postrandomization exclusions:4 Lost to followup: None reported Analyzed: 122 (61 vs. 61)	Age (median): 70 vs. 70 years Male: 80% vs. 64% Race: Not reported Smoking status: Not reported Ta: 70% vs. 72% T1: 20% vs. 23% Tis: 3.3% vs. 0% Tx: 3.3% vs. 3.3% G1: 44% vs. 51% G2: 41% vs. 43% G3: 8.2% vs. 1.6% Gx: 3.3% vs. 0% Primary: 34% vs. 48% Recurrent: 62% vs. 52% Solitary: 21% vs. 21%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Masters, 1999[160] RCT Medium	Recurrence: 44% (27/61) vs. 56% (34/61), HR 0.68 (95% CI 0.41 to 1.13) Recurrence rate: 0.52 vs. 0.58 per patient-year, RR 0.90 (0.58 to 1.52)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Masters, 1999[160] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Masters, 1999[160] RCT Medium	UTI: 31% (19/61) vs. 21% (13/61), RR 1.46 (95% CI 0.79 to 2.69) Bladder spasm: 15% (9/61) vs. 44% (27/61), RR 0.33 (95% CI 0.17 to 0.65) Withdrawal or incomplete therapy due to adverse events: 11% (7/61) vs. 23% (14/61), RR 0.50 (95% CI 0.22 to 1.15)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Matsumura, 1992[75] RCT Medium	Japan Multicenter 1987-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	Not reported	A: Doxorubicin 20 mg/40 ml saline, 21 instillations (following TURBT, once weekly for 2 weeks, then every 2 weeks for 14 weeks, once monthly for 8 months, and once every three months for 1 year) B: Doxorubicin 20 mg/40 ml saline, 6 instillations (over 2 weeks prior to TURBT) C: No doxorubicin

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Matsumura, 1992[75] RCT Medium	Duration, median: 240 days Method: NR	Screened: Not reported Randomized: 443 (182 vs. 126 vs. 135) Postrandomization exclusions: 91 Loss to followup: 26 Analyzed: 284 (126 vs. 75 vs. 83)	Age 50-59: 15% vs. 20% vs. 13% Age 60-69: 34% vs. 32% Vs. 31% Age ≥70: 43% vs. 44% vs. 42% Male: 82% Vs. 79% vs. 84% Race: Not reported Smoking status: Not reported Ta: 33% vs. 35% vs. 33% T1: 43% vs. 35% vs. 36% Tis: 0.8% vs. 2.7% vs. 3.6% Tx: 20% vs. 24% vs. 25% G0: 2.4% vs. 8.0% vs. 2.4% G1: 33% vs. 35% vs. 33% G2: 37% vs. 31% vs. 36% G3: 4.0% vs. 4.0% vs. 0% Gx: 20% vs. 19% vs. 28% Primary: 40% vs. 35% vs. 49% Recurrent: 60% vs. 65% vs. 51% >3 cm: 42% vs. 51% vs. 42% Unifocal: 26% vs. 23% vs. 24% Prior intravesical therapy with doxorubicin: 15% vs. 8% vs. 9.6% Prior intravesical therapy without doxorubicin: 13% vs. 5.3% vs. 6.0% No prior therapy: 53% vs. 69% vs. 64%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Matsumura, 1992[75] RCT Medium	Percent recurrence-free at 1 year: 63.8% vs. 49.0% (p>0.05 for A vs. B) Percent recurrence-free at 2 years: 38.2% vs. 18.8% (p<0.05 for A vs. B)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Matsumura, 1992[75] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsumura, 1992[75] RCT Medium	A vs. B Urinary frequency: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mitsumori, 2004[161] RCT Medium	Japan Multicenter 1998-2001	Recurrent or primary Ta or T1 bladder cancer	Solitary papillary tumor, Tis, uncontrollable UTI, previous muscle-invasive bladder cancer, other malignancy	A: Epirubicin 30 mg/40 ml saline, 6 instillations (starting 1 week after TURBT once every 2 weeks for 12 weeks, total 180 mg) B: Epirubicin 30 mg/40 ml saline, 6 instillations (3 instillations within first 5-7 days after TURBT, then once every 2 weeks for 6 weeks, total 180 mg) C: Epirubicin 30 mg/40 ml saline, 12 instillations (starting 1 week after TURBT, once weekly for 12 weeks, total 360 mg) D: Epirubicin 30 mg/40 ml saline, 12 instillations (3 instillations within first 5-7 days after TURBT, then once weekly for 9 weeks, total 360 mg)
Morales, 1992[162] RCT Low	Canada Single center 1979-1988	Tis or T1 transitional cell carcinoma of the bladder with residual neoplasm; in patients with recurrences must have had a least 2 histologically documented but completely ablated tumors on 2 separate cystoscopic studies in the last 12 months	Not reported	A: Armand Frappier BCG 60 mg weekly for 6 weeks B: Armand Frappier BCG 120 mg weekly for 6 weeks

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mitsumori, 2004[161] RCT Medium	Duration, median: 13.3 months Method: Cystoscopy and urine cytology every 3 months for 3 years, then every 6 months	Screened: Not reported Randomized: 91 Postrandomization exclusions: 15 Loss to followup: 7 Analyzed: 69 (22 vs. 25 vs. 12 vs. 10)	Age (median): 68 years Male: 74% Race: Not reported Smoking status: Not reported Primary: 66% Recurrent: 34% Ta: 62% T1: 38% G1: 15% G2: 64% G3: 21% ≥2 cm: 30% Solitary: 43%
Morales, 1992[162] RCT Low	Duration, mean: 21 months Method: Cystoscopy at 4, 12, and 24 weeks, then at 6 to 12 months	Screened: Not reported Randomized: 97 (49 vs. 48) Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 97	Age: Not reported Sex: Not reported Race: Not reported Smoking status: Not reported Primary or recurrent: Not reported Ta: 44% vs. 45% T1: 15% vs. 16% Tis: 23% vs. 22% Grade: Not reported

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Mitsumori, 2004[161] RCT Medium	Recurrence rates A vs. B vs. C vs. D: 30% (6/20) vs. 25% (6/24) vs. 8.3% (1/12) vs. 0% (0/10) at 6 months, 50% (10/20) vs. 35% (8/23) vs. 45% (4/9) vs. 12% (1/8) at 12 months (p=0.04 for A vs. D with log-rank test, otherwise p>0.05) A or B (180 mg) vs. C or D (360 mg): 27% (12/44) vs. 5% (1/22) at 6 months; 42% (18/43) vs. 29% (5/17) at 12 months (p=0.01, log-rank test) A or C (starting 1 week after TURBT) vs. B or D (early instillations): 22% (7/32) vs. 18% (6/34) at 6 months; 48% (14/29) vs. 29% (9/31) at 12 months (p=0.36, log-rank test) In multivariate regression, total dose (180 vs. 360 mg, AOR 0.32, 95% CI 0.11 to 0.92) and urine cytology (I-II vs. III-IVAOR 3.11, 95% CI 1.08 to 8.94) independent predictors for local recurrence; delayed vs. early not significant (AOR 0.91, 95% CI 0.37 to 2.23)	
Morales, 1992[162] RCT Low	Recurrence-free: 37% (18/49) vs. 67% (32/48), RR 0.55 (95% CI 0.36 to 0.84)	Recurrence-free Ta: 41% (9/22) vs. 67% (14/21), RR 0.61 (95% CI 0.34 to 1.10) T1: 0% (0/8) vs. 56% (5/9), RR 0.10 (95% CI 0.01 to 1.58) Tis: 45% (5/11) vs. 73% (8/11), RR 0.62 (95% CI 0.30 to 1.31)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Mitsumori, 2004[161] RCT Medium		
Morales, 1992[162] RCT Low		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mitsumori, 2004[161] RCT Medium	Side effects (irritated bladder, UTI, or hematuria): 23% (5/22) vs. 24% (6/25) vs. 25% (3/12) vs. 40% (4/10) (P>0.05)	Not reported	
Morales, 1992[162] RCT Low	Side effects (not otherwise defined): 12% (6/49) vs. 33% (16/48), RR 0.37 (95% CI 0.16 to 0.86)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Niijima, 1983[50] RCT (Also Akaza, 1987[49]) Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)
Nomata, 2002[163] RCT Medium	Japan Multicenter 1995-1998	Ta or T1/G1 or G2 transitional cell carcinoma of the bladder, ECOG performance status 0 or 1, age 20 to 80 years, s/p TURBT with no evidence of residual cancer based on cytological evaluation of voided urine	Prior treatment with anthracycline, uncontrollable UTI, prior muscle invasive transitional cell carcinoma, concurrent malignancy, pregnant	A. Epirubicin 30 mg/30 ml saline 19 times over 1 year (once weekly for 4 weeks, then every 2 weeks for 4 months) B. Epirubicin 30 mg/30 ml saline 12 times over 5 months (once weekly for 4 weeks, then every 2 weeks for 4 months, then once per month for 7 months)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Niijima, 1983[50] RCT (Also Akaza, 1987[49]) Medium	Duration: 5 years, maximum; Mean/Median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of installation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (yrs), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race: Not reported Smoking status: NR Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: NR Grade: NR Functional Status: NR Size > 3 cm: 14.8% vs. 74.3% vs. 12.2% vs. 5.0% Proportion with single tumor: 64.4% vs. 63.5% vs. 48.2% vs. 60.4%
Nomata, 2002[163] RCT Medium	Duration, median: 18.1 months Method: Cystoscopy every 3 months	Screened: Not reported Randomized: 138 Postrandomization exclusions: 13 (9 vs. 4) did not meet inclusion criteria Loss to followup: 25% (11/44) vs. 21% (12/58) Analyzed: 125 (55 vs. 70)	Age: Not reported Male: 80% vs. 86% Race: Not reported Smoking status: Not reported Primary: 78% vs. 77% Recurrent: 16% vs. 21% Ta: 51% vs. 60% T1: 45% vs. 37% Tx: 36% vs. 2.9% G1: 49% vs. 53% G2: 51% vs. 47%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Niijima, 1983[50] RCT (Also Akaza, 1987[49]) Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ Recurrence-free survival at 1800 days,* generalized Wilcoxon test: B > D, $p < 0.05$ C > D, $p < 0.05$ Not reported for other treatment group comparisons. * from Akaza, 1987[49]	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, $p < 0.05$ C > D, $p < 0.01$ Comparisons not reported for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as nonsignificant, no p - values reported.
Nomata, 2002[163] RCT Medium	Percent recurrence-free at 3 years: 48.5% vs. 55.1% ($p>0.05$)	Percent recurrence-free at 3 years, G2 bladder cancers: 54% (15/28) vs. 61% (20/33)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Niijima, 1983[50] RCT (Also Akaza, 1987[49]) Medium	A vs. B Recurrence-free survival rate at 540 days: 56.6% vs. 52.0%	NR
Nomata, 2002[163] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Niijima, 1983[50] RCT (Also Akaza, 1987[49]) Medium	A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	
Nomata, 2002[163] RCT Medium	Urinary frequency (grade 1-3): 33% (18/55) vs. 20% (11/55) Dysuria (grade 1-3): 31% (17/55) vs. 21% (15/70) Gross hematuria (grade 1-3): 42% (23/55) vs. 36% (25/70)	Not reported	Reports 59.8% recurrence-free survival for patients with G2 bladder cancer in group B, but doesn't correspond with sample size (33 patients)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Oddens, 2013[164] RCT Medium	Europe Multicenter 1997-2005	Solitary T1G3 or multiple Ta-T1, G1-3 urothelial carcinoma of the bladder	Solitary tumors except T1G3, >10 tumors, CIS, ≥T2, age >83, WHO performance status 3 or 4, previous BCG, intravesical therapy in last 3 months	A: BCG (OncoTICE strain) 5 x 10^8 CFU at 1/3 dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) B: BCG full dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) C: BCG at 1/3 dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36) D: BCG full dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Oddens, 2013[164] RCT Medium	Duration, median: 7.1 years Method: Cystoscopy and cytology every 3 months for 3 years, then every 6 months	Screened: Not reported Randomized: 1805 (450 vs. 453 vs. 450 vs. 452) Postrandomization exclusions:525 (132 vs. 135 vs. 131 vs. 127) Loss to followup: Not reported Analyzed: 1355 (341 vs. 339 vs. 337 vs. 338)	Age (median): 68 vs. 67 vs. 69 vs. 67 years Male: 81% vs. 83% vs. 81% vs. 80% Race: Not reported Smoking status: Not reported Primary: 61% vs. 62% vs. 58% vs. 53% Recurrent: 38% vs. 37% vs. 42% Vs. 46% WHO performance status 2 (excluded >2): 2.3% vs. 1.5% vs. 1.5% vs. 1.8% Unifocal: 15% vs. 14% vs. 13% vs. 11% Ta: 59% vs. 61% vs. 68% vs. 63% T1: 40% vs. 38% vs. 32% vs. 35% G1: 25% vs. 28% vs. 33% vs. 29% G2: 48% vs. 45% vs. 44% Vs. 41% G3: 28% vs. 27% vs. 23% vs. 29% EORTC recurrence score ≤9 (intermediate risk): 69% vs. 71% Vs. 67% Vs. 64% EORTC recurrence score 10-17 (high risk): 22% vs. 22% vs. 27% Vs. 28% EORTC progression score ≤6 (intermediate risk): 27% vs. 30% vs. 32% Vs. 21% EORTC progression score 7-13 (high risk): 51% vs. 52% vs. 53% vs. 60% EORTC progression score 14-23 (high risk): 13% vs. 12% vs. 8.9% vs. 11% Simplified risk group intermediate risk: 56% vs. 56% vs. 65% vs. 56^ Simplified risk group high risk (T1 and/or G3): 44% vs. 43% vs. 35% vs. 43%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Oddens, 2013[164] RCT Medium	Recurrence: 49% (168/341) 43% (145/339) vs. 43% (145/337) vs. 39% (131/338) Percent recurrence-free at 5 years: 54% vs. 59% vs. 63% vs. 64% (unable to reject null hypothesis of inferiority of 1/3 dose or 1 year of treatment; >10% decrease was only observed for A vs. D, HR 0.75, 95% CI 0.59 to 0.94); 59% vs. 62% for A or C (1/3 dose) vs. B or D (full dose) (p=0.09); 57% for A or B (1 year maintenance) vs. 63% for C or D (3 years maintenance) (p=0.06) Progression to ≥T2: 7.6% (26/341) vs. 9.1% (31/339) vs. 8.9% (30/337) vs. 6.5% (22/338) Distant metastasis: 4.4% (15/341) vs. 4.7% (16/339) vs. 5.3% (18/337) vs. 5.3% (18/338) Mortality: 24% (83/341) vs. 26% (88/339) vs. 30% (101/337) vs. 29% (97/338) Bladder cancer mortality: 3.8% (13/341) vs. 5.9% (20/339) vs. 5.0% (17/337) vs. 5.3% (18/338)	1/3 dose (A or C) vs. full dose (B or D) No differences in recurrence-free rates, time to progression, or overall duration of survival when stratified by simplified risk group 3 years (C or D) vs. 1 year (A or B) maintenance, recurrence-free rate Intermediate-risk, 1/3 dose (C vs. A): HR 1.35, 95% CI 1.03 to 1.79 Intermediate-risk, full dose (D vs. B): HR 0.88, 95% CI 0.64 to 1.21 High-risk, 1/3 dose (C vs. A): HR 1.01, 95% CI 0.69 to 1.47 High risk, full dose (D vs. B): HR 1.61, 95% CI 1.13 to 2.30 Time to progression or overall duration of survival: No differences D

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Oddens, 2013[164] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Oddens, 2013[164] RCT Medium	Systemic or local side effects within first year: 7.2% (24/334) vs. 7.0% (23/329) vs. 5.3% (7/323) vs. 5.5% (18/330) Systemic or local side effects after the first year: 0% (0/334) vs. 0% (0/329) vs. 2.8% (9/323) vs. 3.6% (12/330) No differences for A or C vs. B or D, or A or B vs. C or D	National Cancer Institute and from the Kankerbestrijding/KQF through the EORTC Charitable Trust	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ojea, 2007[130] RCT Medium	Spain Multicenter 1995-1998	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	TaG1 tumors; concurrent or previous muscle-invasive disease; concurrent or previous tumor in upper urinary tract or prostatic urethra, intravesical treatment with MMC or BCG during previous 6 months; another malignancy except basal cell carcinoma of skin; previous pelvic irradiation	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. Mitomycin C: 30 mg
Okamura, 1998[165] RCT Medium	Japan Multicenter 1991-1993	Ta-T1 papillary bladder cancer resectable by TURBT, ECOG performance status 0 or 1, age <85 years; primary or recurrent bladder cancer if recurrence-free interval >1 year	Treatment with mitomycin C within 56 weeks, prior T2-T4 bladder cancer, concurrent cancer, pregnant, WBC <4000/mm3, platelets <100,000/mm3, Cr ≥2.0 mg/dL, Karnofsky performance score <50	A: Epirubicin 40 mg/40 ml saline 17 times (within 24 hours of TURBT, during first week, once weekly for 4 weeks, then once monthly for 11 months) B: Epirubicin 40 mg/40 ml saline 6 times (within 24 hours of TURBT, during first week, then once weekly for 4 weeks)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ojea, 2007[130] RCT Medium	Duration, median: 57 months vs 61 months vs 53 months Method: Cystoscopy every 3 months during first year and then every 4 months for the next 4 years	Screened: Not reported Randomized: 430 Postrandomization exclusion: 33 patients did not complete treatment and were withdrawn from study but were followed for recurrence and other end points Loss to followup: Not reported Analyzed: 397 (125 vs135 vs 137)	Age (mean): 65 vs 65 vs 64 Male: 88% vs 86% vs 87% Race: Not reported Smoking: Not reported Stage: 16% vs 14% vs 9% TaG2 22% vs 23% vs 23% T1G1
Okamura, 1998[165] RCT Medium	Duration, median: 29.6 months Cystoscopy and cytology at 4 weeks, then every 3 months	Screened: Not reported Randomized: 148 (74 vs. 74) Postrandomization exclusions: 10 (5 vs. 5) Loss to followup: Not reported Analyzed: 138 (69 vs. 69)	Age (mean): 64 vs. 61 years Male: 78% vs. 81% Race: Not reported Smoking status: Not reported Primary: 77% vs. 80% Recurrent: 23% vs. 20% Ta: 87% vs. 91% T1: 7.2% vs. 8.7% Tis: 5.8% vs. 0% G1: 55% vs. 43% G2: 39% vs. 48% G3: 5.8% vs. 8.7% Size ≥3 cm: 13% vs. 13% Single tumor: 65% vs. 70%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ojea, 2007[130] RCT Medium	A vs. B Recurrence: 27% (38/142) vs 36% (50/139), RR 0.74 (95% CI 0.52 to 1.06) Disease-free interval (B vs. A): HR 1.35, (95% CI 0.89 to 2.06), adjusted HR 1.49 (95% CI 0.97 to 2.28) Recurrence rate: 0.58 vs. 0.74 per 100 patient-months Progression: 10% (14/142) vs. 13% (18/139), RR 0.76 (95% CI 0.39 to 1.47) Time to progression (B vs. A): HR 1.16 (95% CI 0.57 to 2.34) All-cause mortality: 9.2% (13/142) vs. 12% (17/139), RR 0.75 (95% CI 0.38 to 1.48) Bladder cancer death: 2.1% (3/142) vs. 3.6% (5/139), RR 0.59 (95% CI 0.14 to 2.41) Cancer-specific survival time (B vs. A): HR 1.60 (95% CI 0.38 to 6.72)	
Okamura, 1998[165] RCT Medium	Percent recurrence-free at 3 years: 75.1% vs. 77.2% (p=0.62) Time to first recurrence (mean, months): 36.0 vs. 36.9 % disease progression at 3 years: 2.9% (2/69) vs. 1.4% (1/69)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Ojea, 2007[130] RCT Medium		
Okamura, 1998[165] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ojea, 2007[130] RCT Medium	A vs. B Withdrawals due to AE: Not reported Local toxicity 65% vs 64% Systemic toxicity: 11% vs 11%	NR	
Okamura, 1998[165] RCT Medium	Dysuria: 7.2% overall Gross hematuria: 0.7% overall Withdrawal due to adverse events: 1.4% (2/138) Local toxicity: No difference between groups	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Pagano, 1995[132] RCT Low Bassi, 1992[133] Abstract of interim results	Italy Single Center 1990	Multiple papillary tumors (Ta-T1) and CIS	Not reported	6-week course of intravesical therapy: A. Pasteur strain BCG 75 mg B. Pasteur strain BCG 150 mg
Rubben, 1988[141] RCT Medium	Germany Single center 1979-1981	Primary or recurrent NMIBC, any grade	Bimanual palpable tumor after TURBT, previous radiotherapy, intravesical chemotherapy within 6 months, other malignancy	A: Doxorubicin 50 mg/50 ml saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) B: Doxorubicin 50 mg/50 ml saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months) C: No intravesical therapy
Saika, 2010[88] RCT Medium	Japan Multicenter Study years: April 1995 - January 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥ 20 years.	Concurrent or previous CIS; Concurrent or previous urinary tract cancer; Concurrent or previous muscle invasive disease; Lethal disease.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (< 1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Pagano, 1995[132] RCT Low Bassi, 1992[133] Abstract of interim results	Duration: NR Method: NR	Screened: Not reported Randomized: Not reported Postrandomization exclusions: None reported Loss to followup: None reported Analyzed: 183 (90 vs 93)	Not reported
Rubben, 1988[141] RCT Medium	Duration: Mean, median not reported Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months	Screened: Not reported Randomized: 268 (91 vs. 88 vs. 89) Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 220 (79 vs. 59 vs. 82)	Age (mean): 64 vs. 64 vs. 68 years Male: 79% vs. 79% vs. 77% Race: Not reported Smoking status: Not reported Primary: 75% vs. 67% vs. 74% Recurrent: 25% vs. 33% vs. 26% Ta: 84% vs. 81% vs. 77% T1: 16% vs. 19% vs. 23% G1: 60% vs. 65% vs. 59% G2: 36% vs. 28% vs. 34% G3: 7.0% vs. 4.0% vs. 7.2% >3 cm: 19% vs. 15% vs. 24% Solitary: 69% vs. 66% vs. 82%
Saika, 2010[88] RCT Medium	Duration, median: Overall: 44 months; A vs. B vs. C: 44 vs. 46 vs. 42 Method: Cystoscopy every 3 months for 2 years and every 6 months thereafter.	Screened: NR Randomized: 303 Postrandomization exclusions: 21 Eligible: 257 (83 vs. 90 vs. 84) Lost to followup: 17 Total analyzed: 240 (79 vs. 84 vs. 77)	A vs. B vs. C Median age, years: 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Race: NR Recurrent bladder cancer: 40% vs. 43% vs. 40% Stage Ta: 54% vs. 60% vs. 64% Stage T1: 46% vs. 40% vs. 36% Grade G1: 25% vs. 33% vs. 31% Grade G2: 59% vs. 47% vs. 52% Grade G3: 14% vs. 20% vs. 17% Functional status: NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Pagano, 1995[132] RCT Low Bassi, 1992[133] Abstract of interim results	Disease free survival Ta: no difference between doses (p=0.55) Disease free survival CIS: favors the low dose group (p<0.001) Disease free survival T1: number of patients enrolled to date does not allow a statistical conclusion (p=0.07)	
Rubben, 1988[141] RCT Medium	All-cause mortality: 6.7% vs. 1.8% vs. 13.3% (p>0.35) Bladder cancer mortality: 5.3% vs. 1.8% vs. 7.2% (p>0.35) Recurrence rate: 2.5 vs. 2.3 vs. 2.7 per 100 patient-months (p>0.35) Progression: 16% vs. 11% vs. 12% (p>0.35) Time to recurrence (months): 19 vs. 22 vs. 19 (p>0.1)	Recurrence rate (per 100 patient-months) (p>0.05 in all subgroups) Primary: 2.5 vs. 2.4 vs. 2.3 Recurrent: 2.6 vs. 2.8 vs. 3.9 Solitary: 1.8 vs. 3.0 vs. 2.0 Multiple: 3.6 vs. 3.6 vs. 4.6 <3 cm: 1.9 vs. 3.4 vs. 2.9 >3 cm: 2.7 vs. 2.9 vs. 2.6 Tis negative: 2.3 vs. 3.1 vs. 2.2 Tis positive: 3.2 vs 3.2 vs. 4.4
Saika, 2010[88] RCT Medium	A vs. B Median recurrence-free survival, months: 24 vs. 38 (p>0.05) Progression: 0.0% (0/83) vs. 1.1% (1/90), RR 0.36 (95% CI 0.01 to 8.74)	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Pagano, 1995[132] RCT Low Bassi, 1992[133] Abstract of interim results		
Rubben, 1988[141] RCT Medium		
Saika, 2010[88] RCT Medium	NR	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pagano, 1995[132] RCT Low Bassi, 1992[133] Abstract of interim results	Withdrawals due to AE: Not reported Fever: 18 vs 33, p<0.05 Cystitis: 32 vs 57, p<0.05 Macroscopic hematuria: 13 vs 26, p<0.05	NR	Only interim results
Rubben, 1988[141] RCT Medium	Systemic side effects: None observed Local side effects resulting in incomplete treatment: 11% vs. 33% vs. 11%	Not reported	
Saika, 2010[88] RCT Medium	A vs. B Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p = 0.106 Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)	NR	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Schwaibold, 1997[166] RCT Medium	Germany Single center 1983-1987	Ta, T1, or Tis transitional cell carcinoma of the bladder	Unable to perform instillation due to age, immobility, or lack of cooperation	A: Mitomycin C 20 mg/20 ml saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: Mitomycin C 20 mg/20 ml saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: Mitomycin C 20 mg/20 ml saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 ml saline, 42 instillations (same schedule as A)
Sengiku, 2013[142] RCT Medium	Japan Single Center 2004-2012	Stage Ta/T1 or Tis, multiple tumors and recurrence-free period of 3 months or less		At least 2 weeks after removing as much of visible lesion as possible by TURBT, patients received weekly up to 8 times: A. BCG 80 mg (Tokyo strain) in 40 ml saline B. BCG 81 mg (Connaught strain) in 40 ml saline

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Schwaibold, 1997[166] RCT Medium	Duration, median: 57 months Method: Cystoscopy every 3 months	Screened: Not reported Randomized: 477 Postrandomization exclusions: 29 Loss to followup: 29 Analyzed: 419 (209 vs. 96 vs. 75 vs. 39)	Age (median): 72 vs. 71 vs. 69 vs. 73 Male: 82% vs. 77% vs. 77% vs. 74% Race: Not reported Smoking status: Not reported Primary: 68% vs. 75% vs. 75% vs. 56% Recurrent: 32% vs. 25% vs. 25% vs. 44% Ta: 74% vs. 78% vs. 76% vs. 59% T1: 23% vs. 20% vs. 21% vs. 33% Tis: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% G1: 47% vs. 58% vs. 52% vs. 44% G2: 57% vs. 35% vs. 37% vs. 38% G3: 1.9% vs. 4.2% vs. 8.0% vs. 10% Solitary: Not reported Tumor size: Not reported
Sengiku, 2013[142] RCT Medium	Duration: Method: Cystoscopy and urine cytology every 3 months for first 2 years and every 3-6 months thereafter	Screened: Not reported Randomized: 178 Postrandomizations exclusions (for efficacy): 49 with a history of intravesical BCG therapy or concurrent upper urinary tract tumor or discontinued BCG therapy before 6 doses were excluded Loss to followup: none reported Analyzed: 129: (66 vs 63)	Age (mean): 70 vs 71 Male: 89% vs 76% Race: Not reported Smoking: Not reported Stage: 45% vs 43% Ta 33% vs 33% T1 21% vs 24% Tis Grade: 61% vs 57% High 39% vs 43% Low 26% vs 8% CIS

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Schwaibold, 1997[166] RCT Medium	A vs. B vs. C vs. D Recurrence: 24% (51/209) vs. 18% (17/96) vs. 20% (15/75) vs. 31% (12/39) (p=0.21 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, and grade/Tis); RR for B vs. A 0.53, 95% CI 0.29 to 0.96) Progression: 12% (24/209) vs. 5.2% (5/96) vs. 6.7% (5/75) vs. 18% (7/39) (p=0.01 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, grade/Tis, recurrent cancer); RR for B vs. A 0.06, 95% CI 0.01 to 0.51	Recurrence Primary: 15% (21/142) vs. 12% (9/72) vs. 12% (7/56) vs. 27% (6/22) Recurrent: 45% (30/67) vs. 33% (8/24) vs. 42% (8/19) vs. 35% (6/17) Progression Primary: 4.9% (7/142) vs. 4.2% (3/72) vs. 5.4% (3/56) vs. 18% (4/22) Recurrent: 25% (17/67) vs. 4.2% (1/24) vs. 10% (2/19) vs. 18% (3/17), RR for B vs. A 5.1, 95% CI 1.2 to 23 Recurrence rate (per 100 patient-months) Primary: 2.11 vs. 1.52 vs. 1.00 vs. 0.80 Recurrent: 0.54 vs. 0.49 vs. 0.27 vs. 0.91
Sengiku, 2013[142] RCT Medium	Percent recurrence-free: 73% vs. 69% at 2 years, 62% vs. 56% at 5 years (p=0.75)	Percent recurrence-free Ta/T1 without CIS (n=78): 77.6% vs. 62.6% at 2 years, 69.0% vs. 42.6% at 5 years (p=0.22) Complete response (negative urine cytology and random biopsies) Ta/T1 with CIS (n=51): 90% (28/31) vs. 85% (17/20) (p=0.90)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Schwaibold, 1997[166] RCT Medium		
Sengiku, 2013[142] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Schwaibold, 1997[166] RCT Medium	Not reported	Not reported	Reported RR for recurrence, B vs. A, appears much lower than expected based on crude rates, even if adjusted
Sengiku, 2013[142] RCT Medium	Withdrawals due to AE: 7 (8%) vs 9 (10%) Fever AE or complication events: 12 vs 10 Cystitis AE or complication events: 33 vs 28 Hematuria AE or complication events: 8 vs 12	NR	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Serretta, 2010[167] RCT Medium	Italy Multicenter 2002-2003	Multiple and recurrent Ta tumors; recurrent, single or multiple T1 tumors	Single and primary Ta/T1 G1/G2 tumors, concomitant or previous Tisand/or T1G3, lesions >3 cm, previous BCG, previous doxorubicin or epirubicin, other intravesical therapy in last 12 months, previous radiotherapy and/or systemic chemotherapy	A: Epirubicin 80 mg/50 ml saline, 16 instillations (within 6 hours of TURBT, then once weekly for 5 weeks, once weekly for 10 months) B: Epirubicin 80 mg/50 ml saline, 6 instillations (within 6 hours of TURBT, then once weekly for 5 weeks)
Tolley, 1996[91] RCT Medium	United Kingdom Multicenter Study years: March 1984 - December 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	CIS alone	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes. B: Mitomycin C 40 mg (in 40 mL water), installation within 24 hours of TURBT; retained for 60 minutes. Additional installations (same dose) every 3 months x 1 year (total 5 installations). C: No adjuvant treatment. TURBT alone.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Serretta, 2010[167] RCT Medium	Duration, median: 48 months Method: Cystoscopy and cytology every 3 months for 2 years, then 6 months from years 3 to 5	Screened: 577 Randomized: 482 (245 vs. 237) Postrandomization exclusions: Not reported Loss to followup: 87 (43 vs. 44) Analyzed: 395 (185 vs. 210)	Age (median): 69 vs. 68 years Male: 89% vs. 84% Race: Not reported Smoking status: Not reported Primary: 62% vs. 58% Recurrent: 38% vs. 42% Single: 34% vs. 34% Multiple: 66% vs. 66^ TaG1-2: 37% Vs. 35% T1G1: 24% vs. 21% T1G2: 39% vs. 44%
Tolley, 1996[91] RCT Medium	Duration, median: (A and B, not reported for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: 502 Randomized: 452 Postrandomization exclusions: NR Lost to followup: 5* (2 vs. 1 vs. 2) Total analyzed: 452 (149 vs. 146 vs. 157) * reportedly with no followup data, but included in ITT analyses	A vs. B vs. C Age 24-50: 13% vs. 9% vs. 9% Age 51-60: 24% vs. 23% vs. 29% Age 61-70: 36% vs. 37% vs. 34% Age 71-80: 23% vs. 30% vs. 25% Age 81-100: 4% vs. 1% vs. 3% Male: NR Race: NR Stage Ta: 50% vs. 52% vs. 56% Stage T1: 48% vs. 50% vs. 43% Grade 1: 37% vs. 34% vs. 45% Grade 2: 52% vs. 55% vs. 46% Grade 3: 10% vs. 10% vs. 8%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
Serretta, 2010[167] RCT Medium	Percent recurrence-free at 3 months: 98.4% (182/185) vs. 94.8% (199/210) (p=0.06) Percent recurrence-free at 6 months: 95.1% (174/183) vs. 87.3% (157/180) (p=0.004) Percent recurrence-free at 12 months: 86.7% (143/165) vs. 79.1% (136/172) (p=0.03) Percent recurrence-free at 18 months: 77.8% (105/135) vs. 68.1% (98/144) (p=0.03) Percent recurrence-free at 24 months: 70.2% (87/124) vs. 63.0% (85/135) (p=0.11) Percent recurrence-free at 36 months: 62.1% (72/116) vs. 54.4% (69/127) (p=0.11) Percent recurrence-free at 48 months: 50.5% (48/95) vs. 45.9% (51/111) (p=0.26) Time to recurrence (median, months): 17 vs. 12 (p=0.10) Progression to muscle-invasive: 2.9% (7/245) vs. 1.3% (3/237)	Percent recurrence-free at 12 months Primary: 91.4% vs. 82.6% (p=0.03) Recurrent: 82.3% vs. 77.1% (p=0.67) Single: 87.1% vs. 83.9% (p=0.45) Multiple: 88.3% vs. 78.4% (p=0.08) Ta: 88.8% vs. 81.6% (p=0.10) T1: 87.4% vs. 79.7% (p=0.28) G1: 92.6 vs. 78.3% (p=0.05) G2: 84.9% vs. 81.6% (p=0.41)
Tolley, 1996[91] RCT Medium	**A vs. B** Recurrence at 24 months: 42% vs. 31% (p = 0.14) Recurrence-free interval, group comparisons, HR 0.74 (95% CI 0.51 to 1.06) Progression-free interval, group comparisons, HR 0.97 (95% CI 0.46 to 2.06) All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146), RR 0.79 (95% CI 0.59 to 1.1) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146), RR 0.98 (95% CI 0.38 to 2.5)	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Serretta, 2010[167] RCT Medium		
Tolley, 1996[91] RCT Medium	NR	NR

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Serretta, 2010[167] RCT Medium	Serious adverse events: 0.2% overall Chemical cystitis with discontinuation of treatments: 0.4% overall Fever: 2.2% overall Dysuria and urgency resulting in treatment interruption: 7.1% overall Hematuria: 2.9% overall Treatment postponement: 15.7% overall	Not reported	
Tolley, 1996[91] RCT Medium	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146), RR 0.05 (95% CI 0.003 to 0.88) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was not reported as a side effect by any patient in either group.	NR	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Turkeri, 2010[168] RCT Medium	Turkey Multicenter 2002-2004	Primary bladder tumor, ≤3 lesions, Ta (G2 or G3) or T1 (G1 or G2)	Tis, incomplete TURBT, tumor in the urethra or upper urinary tract, other malignancy, >80 years of age, WHO performance score >2; instillation >18 hours after TURBT	A: Epirubicin 100 mg within 6 hours after TURBT B: Epirubicin 100 mg within 6 hours and 12-hours after TURBT

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Turkeri, 2010[168] RCT Medium	Duration, mean: 16.9 months Method: Cystoscopy every 3 months for 1 year, then every 6 months during years 2 and 3, then once yearly	Screened: Not reported Randomized: 299 Postrandomization exclusions: Not reported Loss to followup: Not reported Analyzed: 143 (68 vs. 75)	Mean age: 59 vs. 62 years Male: Not reported Race: Not reported Smoking status: Not reported Primary: 85% vs. 79% Recurrent: 15% vs. 21% Ta: 54% vs. 52% T1: 46% vs. 48% G1: 19% vs. 17% G2: 78% vs. 80% G3: 2.9% vs. 2.7%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Turkeri, 2010[168] RCT Medium	Recurrence rates: 14.7% vs. 21.3%, adjusted HR 0.67 (95% CI 0.30 to 1.51) (adjusted for grade, stage, solitary vs. multiple, age <70 vs. ≥70 years) Progression: 1.5% (1/68) vs. 4.0% (3/75), RR 0.37 (95% CI 0.04 to 3.45) Recurrence-free survival (months): 10.3 vs. 10.5 months (p=0.47, log-rank) Disease-free survival (months): 14.9 vs. 15.5 months	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Turkeri, 2010[168] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Turkeri, 2010[168] RCT Medium	Not reported	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ueda, 1992[169] RCT Medium	Japan Multicenter 1984-1986	Ta and T1 transitional cell carcinoma of bladder	Incomplete resection with recurrence within first month	A: Doxorubicin 30 mg/30 ml saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) B: Doxorubicin 30 mg/30 ml saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week C: Doxorubicin 30 mg/30 ml saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) D: Doxorubicin 30 mg/30 ml saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ueda, 1992[169] RCT Medium	Duration, mean: 31 months Method: Cystoscopy at 4 weeks then every 3 months	Screened: Not reported Randomized: 275 (68 vs. 67 vs. 70 vs. 70) Postrandomization exclusions: 51 (18 vs. 12 vs. 12 vs. 9) Loss to followup: 37 (10 vs. 11 vs. 5 vs. 11) Analyzed: 187 (40 vs. 44 vs. 53 vs. 50)	Mean age: 64 vs. 66 vs. 63 vs. 60 years Male: 72% vs. 82% vs. 83% vs. 78% Race: Not reported Smoking status: Not reported Primary: 70% vs. 77% vs. 75% vs. 70% Recurrent: 30% vs. 23% vs. 25% vs. 30% Ta: 55% vs. 50% vs. 47% vs. 68% T1: 40% vs. 34% vs. 40% vs. 28% Tx: 5.0% vs. 16% vs. 13% vs. 4.0% G1: 35% Vs. 34% vs. 23% vs. 42% G2: 55% vs. 52% vs. 62% Vs. 40% G3: 10% vs. 14% vs. 9.4% vs. 18% >3 cm: 7.5% vs. 9.1% vs. 5.7% vs. 14% Solitary: 52% vs. 48% vs. 57% vs. 48%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Ueda, 1992[169] RCT Medium	Percent recurrence-free at 36 months: 79.4% vs. 73.7% vs. 67.6% vs. 63.1% (NS); 76.4% vs. 65.4% for A + B vs. C +D (p>0.05)	Higher recurrence-free rate in early therapy groups (A + B) vs. delayed therapy groups (C + D) for primary tumors, Ta, <1 cm, G1, multiple tumors, G2

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Ueda, 1992[169] RCT Medium		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ueda, 1992[169] RCT Medium	Bladder irritation: 48% (24/50) vs. 55% (30/55) vs. 26% (15/58) vs. 26% (16/61) Bladder irritation resulting in withdrawal: 8% (4/50) vs. 5% (3/55) vs. 2% (1/58) vs. 3% (2/61) Hematuria and bladder calculi: 0 vs. 0 vs. 0 vs. 2% (1/61)	Not reported	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Europe Multicenter 1992-1997	Intermediate or high risk superficial bladder tumors; single or multiple, primary or recurrent, completely resectable stages Ta-T1, G1 to G3, biopsy proven TCC	Primary solitary tumor, T2 or greater, CIS, age>85, previously treated with doxorubicin, epirubicin, or BCG, intravesical treatment during previous 3 months	A. Epirubicin 50 mg in 50 ml saline weekly for 6 consecutive weeks starting within 24 hours of transurethral resection B. BCG 5x10^8 CFU (Tice strain) for 6 consecutive weeks starting 7-15 days after transurethral resection C. BCG + isoniazid: BCG 5x10^8 CFU (Tice) for 6 consecutive weeks starting 7-15 days after transurethral resection plus 300 mg INH orally the day before, same day and day after instillation Median duration of treatment: 12 months vs 18 months vs 12 months

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Duration, median: 4 years (initial report); 9 years (subsequent report) Method: Cystoscopy and urine cytology every 3 months during first 3 years and then every 6 months	Screened: Not reported Randomized: 957 postrandomization exclusions: 120 (32 had no tumor, 31 had muscle invasive tumor, 37 had CIS, 20 ineligible for other reasons) Loss to followup: 169 prematurely stopped treatment due to concomitant disease, refusal or loss to followup. In another 137 patients further followup data were required Analyzed: 837 (279 vs 281 vs 277)	Age (mean): 67 vs 66 vs 66 Male: 79% vs 75% vs 78% Race: Not reported Smoking: Not reported Stage: Ta: 63% vs 60% vs 63% T1: 33% vs 37% vs 35% Grade 1: 38% vs 37% vs 36% Grade 2: 48% vs 47% vs 49% Grade 3: 11% vs 13% vs 12%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year **Study Name** **Study Design** **Risk of Bias**	**Results (report n/N when possible): This will primarily be recurrence, progression, survival**	**Results:** **According to Tumor Characteristics (KQ3 b)**
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Recurrence at 3 years: 51% vs 35% vs 36% Time to first recurrence at 3.5 years: BCG with or without INH significantly prolonged time to first recurrence vs Epirubicin Progression to muscle invasive disease: 7% (19/279) vs 3% (9/281) vs 5% (15/277) Death at 3.9 years: 19% vs 15% vs 19% Death due to bladder cancer: 4% vs 2% vs 3% <u>9 year followup:</u> Recurrence: 53% vs 37% vs 40% Progression: 9% vs 7% vs 8% Death: 38% vs 30% vs 32% Death due to bladder cancer: 7% vs 3% vs 4% With BCG arms pooled (epirubicin vs BCG) hazard ratios (combines intermediate and high risk: Recurrence: 0.62 (0.50 to 0.76) Progression: 0.84 (0.51 to 1.39) Death: 0.76 (0.59 to 0.96) Death due to bladder cancer: 0.47 (0.25 to 0.89)	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)		

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
van der Meijden, 2001[144] RCT Medium Sylvester, 2010[145] (9 year followup)	Withdrawals due to AE: 16 (6%) vs 31 (12%) vs 44 (17%) Bacterial cystitis: 26% vs 26% vs 23% Chemical cystitis 31% vs 42% vs 45% Macroscopic hematuria: 17% vs 35% vs 30%	National Cancer Institute	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147] RCT	The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Previous local or systemic cancer therapy or radiotherapy	A. MMC 30mg in 50ml saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50ml saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147] RCT	Duration, median: 32 months Method: Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter	Screened: Not reported Randomized: 469 (156 vs 154 vs 159) postrandomization exclusions: 17 (ineligible) Loss to followup: None reported although 15 patients excluded for "different reasons" Analyzed: 437 (148 vs 140 vs 149)	Age (mean): 66 vs 66 vs 66 years Male: 80% vs 86% vs 87% Race: Not reported Smoking status: Not reported G1: 16% vs 20% vs 22% pTaG2: 37% vs 34% vs 36% G3: 4% vs 4% vs 3% CIS: 8% vs 16% vs 10%

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results (report n/N when possible): This will primarily be recurrence, progression, survival	Results: According to Tumor Characteristics (KQ3 b)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147] RCT	B vs. C % Recurrence-free, all papillary tumors 1 yr: 68% vs 69% 2 yr: 54% vs 62% 5 yr: 36% vs 54% (log-rank, p=0.07) Recurrence: 64% (75/117) vs. 46% (62/134), RR 1.39 (95% CI 1.10 to 1.74) Progression: 5% (7) vs. 6% (8)	B vs C % Disease-free, G3 papillary tumors 1 yr: 55% vs 64% 2 yr: 46% vs 50% Complete response (negative cystoscopy, cytology, and biopsies), CIS: 70% (16/23) vs 47% (7/16), RR 1.59 (95% CI 0.86 to 2.95)

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Results: According to Dosing Frequency, Duration of Treatment, and/or Timing of Administration (KQ3 c)	Results: According to Patient Characteristics (KQ3 e)
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147] RCT	NR	

Appendix E4. Key Question 3c: Dose and Duration of Randomized Controlled Trials

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Witjes, 1993[146] RCT Medium The Dutch Cooperative Trial Witjes, 1996[147] RCT	B vs. C Drug-induced cystitis: 30% (42/140) vs 32% (48/149) Drug-induced cystitis requiring treatment delay or discontinuation: 1.4% (2/140) vs. 2.0% (3/149) Systemic side-effects: 27% (38/140) vs 18% (27/149) Systemic side-effects requiring treatment delay or discontinuation: 4.3% (6/140) vs. 2.0% (3/149) Withdrawals due to AE: 14 (total across 3 arms) Intercurrent death=10 (total across 3 arms)		

AE, Adverse Events; AOR, adjusted odds ratio; BCG, bacillus Calmette-Guérin; BUN, blood urea nitrogen; CFU, colony forming unit; CI, confidence interval; CIS, carcinoma in situ; cm, centimeter; Cr, serum creatinine level; DNA, Deoxyribonucleic acid; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; g, grams; G1, Grade 1; G2, Grade 2; G3, Grade 3; HR, Hazard Ratio; IA, intra-arterial; INH, isoniazid; ITT, intention-to-treat analysis; IU, International unit; IV, intravenous; MBIC, Muscle Invasive Bladder Cancer; mg, milligram; mg/dL, milligram per deciliter; mL, millileter; ml, millileter; MMC, Mitomycin C; MU, Million units; NMIBC, Non-Muscle Invasive Bladder Cancer; NR, Not Reported; NS, Not significant; pT1, Tumor stage 1 determined by pathology; pT2, Tumor stage 2 determined by pathology; pTa, Tumor stage 3 determined by pathology; RCT, Randomized Controlled Trial; RFS, Recurrence free survival; RR, Relative Risk; SD, Standard deviation; T1, Tumor stage 1; T2, Tumor stage 2; Ta, Tumor stage a; TCC, Transitional cell carcinoma; Tis, carcinoma in situ; TURBT, Transurethral resection of bladder tumour; Tx, Tumor stage unknown; UTIs, Urinary Tract Infections; WBC, White blood cells; WHO, World Health Organization; yr(s), year(s)

Appendix E5. Key Question 4: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Harland, 2007[170] RCT Medium	United Kingdom Multicenter 1991-2003	Diagnosed with pT1G3 NX M0 tumor or tumors of the bladder in the previous 6 months; muscle from base of tumor was histologically clear; all visible tumors resected transurethrally	Prior therapy with intravesical chemotherapy or BCG (other than a single adjuvant treatment)	Group 1: Patients with single tumors and no carcinoma *in situ* A: Observation, no treatments given other than TURBT before 3 month cystoscopy (n=38) B: Radiation therapy, 60 Gy in 30 fractions during 6 weeks (n=39) Group 2: Patients with multiple tumors or carcinoma *in situ* C: Radiation therapy, 60 Gy in 30 fractions during 6 weeks (n=65) D: Intravesical therapy, clinician preference for either Mitomycin C, 40 mg in 40 ml water, weekly for 6 weeks OR BCG approximately 109 viable organisms in 50 ml normal saline, weekly for 6 weeks A second course of 6 BCG instillations could be given if followup biopsy was positive. After initial treatment period clinicians were free to treat patients as they thought appropriate	Duration: Median followup in survivors: 44 months Method: Cystoscopy at 3, 6,9 and 12 months after randomization, then at least annually
Mulders, 1994[171] Retrospective Cohort High	The Netherlands 1983-1988	T1G3 tumors	Not Reported	A: TURBT only B: TURBT + intravesical therapy with 30mg Mitomycin C in 50 ml saline once per week for one month and then once per month for a total of 6 months OR BCG given once per week for 6 consecutive weeks C: TURBT + external beam radiation therapy with 44 Gy on the pelvic region and 66 Gy boost on the bladder region	Duration (Median): 4 years Method: Not reported

Appendix E5. Key Question 4: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Harland, 2007[170] RCT Medium	Screened: Not reported Randomized: 210 (38 vs. 38 vs. 65 vs. 68) Post-randomization exclusions: 6, pT2 at diagnosis Lost to followup: 7 Analyzed: 204 (38 vs. 38 vs. 64 vs. 64)	Age (median): 70 vs. 69 vs. 70 vs. 68 years Male: 84% vs. 92% vs. 84% vs. 81% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Largest Tumor Diameter <2cm: 56% vs. 53% vs. 69% vs. 72% Functional status:	A,B,D vs. C: Hazard Ratio (95% CI) Progression-free interval: 1.0 (0.65-1.74) Progression-free survival: 1.35 (0.92-1.98) Overall survival: 1.32 (0.86-2.04) Recurrence-free interval: 0.77 (0.54-1.10) Recurrence-free survival: 0.94 (0.67-1.30)	A vs. D vs. B,C: Urinary frequency: 4/38 vs. 1/6 vs. 8/102 Cystitis: 1/38 vs. 0 vs. 2/102	Not Reported	
Mulders, 1994[171] Retrospective Cohort High	Screened: 155 Randomized: Not applicable, non randomized study Post-randomization exclusions: Not applicable, non randomized study Lost to followup: Not reported Analyzed: 121 (48 vs. 51 vs. 17)	Age (years): ≥ 70: 51%; <70: 49% Male: 86% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 0 Single tumor only: 61% Functional status: Not reported	Median time to first recurrence (months): 11 vs. 19 vs. 25; P<0.05 for A vs. B,C; B vs C not significantly different Recurrence during followup: 75% vs. 55% vs. 35%; P<0.05 for A vs. B,C; B vs C not significantly different	Not Reported	Not Reported	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Babjuk, 2005[172] High	Czech Republic Single center 2001-2003	Patients with suspected primary or recurrent superficial urinary bladder cancers	History of surgical or instillation intravesical therapy within the previous 3 months	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=60) B: White light cystoscopy with TURBT (n=62) All patients with G1 or G2 tumors received adjuvant intravesical therapy; all patients with G3 tumors received intravesical BCG
Dragoescu, 2011[173] Medium	Romania Single center 2009	Patients with NMIBC	Not stated	A: White light and HAL fluorescent cystoscopy with TURBT B: White light cystoscopy with TURBT All patients received postoperative intravesical epirubicin (Farmorubicin) and additional therapy based on risk group

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Babjuk, 2005[172] High	24 months, followup with white light cystoscopy	Screened: Not reported Randomized: 128 (64 vs. 64) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 122 (60 vs. 62)	Age (mean): 68 vs. 70 years Male: 72% vs. 63% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 67% vs. 55% Stage: 63% vs. 60% Ta, 37% vs. 40% T1 Grade: 50% vs. 53% G1, 40% vs. 35% G2, 10% vs. 11% G3	A vs. B Recurrence at 10-15 weeks: 8% (5/60) vs. 37% (23/62) Recurrence-free (n=60 and 62): 66% vs. 39% at 12 months, 40% vs. 28% at 24 months Median time to recurrence: 14 vs. 4 months (p=0.008, log-rank test) Recurrence-free, multiple tumors (n=45 and 38): 62% vs. 32% at 12 months, 39% vs. 13% at 24 months (p=0.001, log-rank test) Recurrence-free, solitary tumors (n=15 and 24): 80% vs. 52% at 12 months, 46% vs. 48% at 24 months (p=0.47, log-rank test) Recurrence-free, primary tumors (n=20 and 28): 85% vs. 46% at 12 months, 39% vs. 34% at 24 months (p=0.13, log-rank test) Recurrence-free, recurrent tumors (n=40 and 34): 57% vs. 33% at 12 months, 40% vs. 23% at 24 months (p=0.02, log-rank test) Progression through 15 months: 8.3% (5/60) vs. 8.1% (5/62)
Dragoescu, 2011[173] Medium	12 months, followup cystoscopy method not reported	Screened: Not reported Randomized: 57 (27 vs. 35) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 44 (22 vs. 22)	Age (mean): 59 vs. 62 years Male: 78% Race: Not reported Smoker: 73% vs. 64% Recurrent bladder cancer: Not reported Stage: 22% vs. 18% Ta, 78% vs. 82% T1 Grade: 32% vs. 27% G1, 55% vs. 64% G2, 14% vs. 9.1% G3	A vs. B Recurrence at 3 months: 4.6% (1/22) vs. 14% (3/22) Recurrence at 6 months: 9.1% (2/22) vs. 23% (5/22) Recurrence at 12 months: 18% (4/22) vs. 45% (10/22), HR 0.33 (95% CI 0.11 to 0.98)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Babjuk, 2005[172] High	Not reported	Czech Health Ministry	
Dragoescu, 2011[173] Medium	Not reported	National Exploratory Research Project Program	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Filbeck, 2002[174] (also Denzinger 2007[175], Denzinger 2007[176]) Medium	Germany Single center 1997-2000	Patients suspected of having bladder cancer on preoperative endoscopy	Not stated	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=88) B: White light cystoscopy with TURBT (n=103) All patients received intravesical prophylaxis based on AUA guidelines according to number of tumors, stage, and grade

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Filbeck, 2002[174] (also Denzinger 2007[175], Denzinger 2007[176]) Medium	Mean 21 months, followup cystoscopy method not reported	Screened: Not reported Randomized: 301 (151 vs. 150) Post-randomization exclusions: None reported Loss to followup: 4 (2 vs. 2) Analyzed for recurrence (NMIBC): 191 (88 vs. 103)	Age (median): 68 vs. 70 years Sex: Not reported Race: Not reported Smoker: Not reported Recurrent bladder cancer: 31% vs. 18% (p=0.06) Stage: 42% vs. 41% pTaG1, 31% vs. 28% pTaG2, 2.3% vs. 1.0% pTaG3, 7.9% vgs. 13% pT1G2, 11.4% vs. 11.7% pT1G3, 5.7% vs. 4.9% CIS Risk group: 35% vs. 48% low, 46% vs. 34% intermediate, 19% vs. 18% high	A vs. B Residual tumor at 6 weeks, overall: 4.5% (4/88) vs. 25% (26/103), RR 0.18 (95% CI 0.07 to 0.47) Residual tumor at 6 weeks, pTa: 3.0% (2/66) vs. 18% (13/73), p=0.006 Residual tumor at 6 weeks, pT1: 12% (2/17) vs. 36% (9/25), p=0.15 Residual tumor at 6 weeks, pTis: 0.0% (0/5) vs. 80% (4/5), p=0.05 Recurrence free (n=88 and 103): 90% vs. 74% at 12 months, 90% vs. 66% at 24 months (p=0.004, log-rank test); adjusted HR 0.33 (95% CI 0.16 to 0.67) (adjusted for prophylaxis and prognostic group) Recurrence free, low risk (n=31 and 50): 92% vs. 88% at 12 months, 92% vs. 78% at 24 months (p=0.25, log-rank test) Recurrence free, intermediate risk (n=40 and 35): 89% vs. 65% at 12 months and 89% vs. 61% at 24 months (p=0.02, log rank test) Recurrence free, high risk (n=17 and 18): 87% vs. 54% at 12 months, 87% vs. 40% at 24 months (p=0.05, log-rank test) Recurrence at complete followup (median 83 vs. 86 months): 16% (18/88) vs. 44% (43/103) Recurrence free: 88% vs. 73% at 2 years, 84% VS. 64% at 4 years, 79% vs. 54% at 6 years, 71% vs. 45% at 8 years; HR 0.36 (95% CI 0.21 to 0.63) Recurrence free, low risk: 98% vs. 84% at 2 years, 95% vs. 72% at 4 years, 81% vs. 45% at 8 years (p=0.003, log-rank test) Recurrence free, intermediate risk: 86% vs. 60% at 2 years, 83% vs. 51% at 4 years, 71% vs. 42% at 8 years (p=0.02, log-rank test) Recurrence free, high risk: 85% vs. 58% at 2 years, 75% vs. 46% at 4 years, 60% vs. 43% at 8 years (p=0.04, log-rank test) Patients with T1 high grade lesions on initial cystoscopy (multifocal, concomitant CIS, >3 cm, n=21 and 25)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Filbeck, 2002[174] (also Denzinger 2007[175], Denzinger 2007[176]) Medium	Not reported	Not reported	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Geavlete, 2010[177] Medium	Romania Single center 2007-2009	Patients suspected of having bladder cancer based on positive urinary cytology and ultrasonographic suspicion of bladder tumor	Massive hematuria, moderate to severe leukocyturia, previous intravesical instillations within 3 months, imaging suggesting upper tract disease	A: White light and HAL fluorescent cystoscopy with TURBT (n=223) B: White light cystoscopy (n=223) All patients received single, immediate postoperative mitomycin-C instillation
Geavlete, 2011[178] Medium	Romania Single center Study years not reported	Patients suspected of having bladder cancer based on positive urinary cytology and ultrasonographic suspicion of bladder tumor	Massive hematuria, moderate to severe leukocyturia, previous intravesical instillations within 3 months, imaging suggesting upper tract disease, previously cystoscopically diagnosed bladder tumor	A: White light and HAL fluorescent cystoscopy with TURBT (n=125) B: White light cystoscopy and TURBT (n=114) All patients received single, immediate postoperative mitomycin-C instillation

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Geavlete, 2010[177] Medium	6 weeks, followup with white light cystoscopy	Screened: Not reported Randomized: 466 (223 vs. 223) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (CIS, pTaG3, pT1): 136 (72 vs. 64)	Age (mean): 64 years (overall) Male: 73% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 10% vs. 8.1% CIS, 51% vs. 47% pTa, 17% vs. 17% pT1, 14% vs. 15% MIBC Grade (for Ta and T1 tumors): 40% vs. 40% G1, 41% vs. 41% G2, 19% vs. 19% G3	A vs. B Recurrence at 6 weeks: 11% (8/72) vs. 31% (20/64), p=0.0001 Recurrence at 6 weeks, high grade tumors: 17% (5/29) vs. 37% (10/27), p=0.018 Recurrence at 6 weeks, solitary papillary tumors < 3 cm: 9.1% (1/11) vs. 20% (2/10), p>0.05 Recurrence at 6 weeks, solitary papillary tumors >3 cm or multiple: 16% (6/38) vs. 36% (13/36), p=0.005 Arm A (blue light), fluorescence cystoscopy vs. standard cystoscopy, detection rates CIS: 96% (22/23) vs. 74% (17/23), p=0.009 pTa: 94% (107/114) vs. 83% (95/114), p=0.001
Geavlete, 2011[178] Medium	2 years, followup with white light cystoscopy	Screened: Not reported Randomized: 362 (181 vs. 181) Post-randomization exclusions: None reported Lost to followup: 30 (17 vs. 13) Analyzed for recurrence (NMIBC): 239 (125 vs. 114)	Age (mean): 67 years (overall) Male: 74% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 11% vs. 8.3% CIS, 45% vs. 41% pTa, 19% vs. 18% pT1 Grade: Not reported	A vs. B Recurrence at 3 months, overall (primary or other): 7.2% (9/125) vs. 16% (18/114), p=0.003 Recurrence at 3 months, primary site: 7.9% (9/114) vs. 5.6% (7/125), p=0.22 Recurrence at 6 months: 12% (15/125) vs. 22% (25/114), p=0.003 Recurrence at 12 months: 22% (27/125) vs. 32% (37/114), p=0.005 Recurrence at 24 months, overall: 31% (39/125) vs. 46% (52/114), p=0.001 Recurrence at 24 months, primary NMIBC: 24% (18/74) vs. 37% (26/70), p=0.014 Recurrence at 24 months, recurrent NMIBC: 41% (21/51) vs. 59% (26/44), p=0.007 Recurrence at 24 months, single tumor NMIBC: 23% (10/43) vs. 35% (18/51), p=0.06 Recurrence at 24 months, multiple tumor NMIBC: 35% (29/82) vs. 54% (34/63), p=0.001 Progression rates: 2.4% (3/125) vs. 4.4% (5/114) at 1 year (p=0.20), 4% (5/125) vs. 7% (8/114) at 2 years (p=0.12)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Geavlete, 2010[177] Medium	Not reported	Not reported	
Geavlete, 2011[178] Medium	"No complications related to HAL instillation"	Not reported	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hermann, 2011[179] Medium	Denmark Two centers Study years not reported	Patients >18 years of age suspected of having Ta/T1 bladder cancer based on cystoscopy	Porphyria, gross hematuria, known allergy to HAL	A: White light and HAL fluorescent cystoscopy with TURBT (n=59) B: White light cystoscopy (n=74) No patient received intravesical therapy immediately after TURBT, 3 patients in each arm had previously received mitomycin and 21 patients BCB (10 in arm A and 11 in arm B)
Karaolides, 2012[180] Medium	Greece Single center 2008-2010	Patients with suspected bladder cancer	Upper urinary tract urothelial or bladder cancer with recurrence within the last 12 months or intravesical chemotherapy or immunotherapy within the last 3 months	A: White light and HAL fluorescent cystoscopy with TURBT (n=41) B: White light cystoscopy with TURBT (n-45) Patients with moderate and high risk tumors received epirubicin 6 weeks after TURBT, or BCG

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Hermann, 2011[179] Medium	12 months, followup with white light cystoscopy	Screened: Not reported Randomized: 233 (115 vs. 118) Underwent allocated procedure: 219 (102 vs. 117) Post-randomization exclusions: 14 (14 vs. 1) Lost to followup: 25 (17 vs. 9) Analyzed for recurrence (Ta or nonsurgical T1): 133 (59 vs. 74)	Age (mean): 71 vs. 69 years Male: 75% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage and grade: 84% vs. 90% Ta low grade, 12% vs. 6% Ta high grade, 0% T1 low grade, 2% vs. 4% T1 high grade	A vs. B Recurrence at 4 months: 17% (10/59) vs. 31% (23/74) Recurrence through 12 months: 31% (18/59) vs. 47% (35/74), p=0.05
Karaolides, 2012[180] Medium	18 months, followup with white light cystoscopy	Screened: 140 Randomized: 102 (49 vs. 53) Received allocated procedure: 88 (42 vs. 46) Post-randomization exclusions: None reported Lost to followup: 2 (1 vs. 1) Analyzed for recurrence (NMIBC): 86 (41 vs. 45)	Age (mean): 66 vs. 64 years Male: 80% vs. 89% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 29% vs. 24% Tumor stage and grade: 12% vs. 6.7% CIS, 22% vs. 31% high grade, 63% vs. 60% low grade, 2.4% vs. 2.2% low malignant potential	A vs. B Recurrence through complete followup (median 18 vs. 14 months): 17% (7/41) vs. 40% (18/45), p=0.02 Recurrence at 3 months: 2.4% (1/41) vs. 13% (6/45), p<0.001 Recurrence free: 91% vs. 56% at 12 months, 82% Vs. 51% at 18 months (p=0.006, log-rank test) Recurrence free, solitary tumors: 93% vs. 77% at 12 months, 74% vs. 77% at 18 months (p=0.35, log-rank test) Recurrence free, multifocal tumors: 89% vs. 27% at 12 months, 90% vs. 14% at 18 months (p<0.001) Recurrence free, primary tumors: 90% vs. 62% at 12 months, 77% vs. 55% at 18 months (p=0.02, log-rank test) Recurrence free, recurrent tumors: 92% vs. 42% at 12 months, 92% vs. 42% at 18 months (p=0.02, log-rank test) Recurrence free, low-grade tumors and low malignant potential lesions: 94% vs. 63% at 12 months, 89% vs. 63% at 18 months (p=0.02, log-rank test) Recurrence free, CIS and high-grade tumors: 84% vs. 43% at 12 months, 73% vs. 34% at 18 months (p=0.01, log-rank test) Progression to MIBC: 0% (0/41) vs. 4.4% (2/45)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Hermann, 2011[179] Medium	A vs. B False-positives: 25% (25/102) (false-positives for fluorescent cystoscopy performed after white light cystoscopy) vs. 16% (19/117)	Photocure, Juchum and Boemske Foundations	
Karaolides, 2012[180] Medium	Not reported	None reported	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Kriegmair, 2002[1] High	Austria Multicenter 1997-1998	Patients suspected of having primary bladder cancer or tumor recurrence	Not stated	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=52) B: White light cystoscopy with TURBT (n=49) Additional treatments not reported
Naselli, 2012[3] Italy Medium	Italy Two centers 2009-2010	Patients with overt or suspected bladder cancer	Not stated	A: Narrow band imaging cystoscopy and TURBT (n=76) B: White light cystoscopy and TURBT (n=72) Additional treatments not reported
O'Brien, 2013[4] Medium	UK Single center 2005-2010	Patients with suspected new NMIBC	Suspected MIBC, porphyria, pregnancy, sensitivity to 5-ALA based intravesical photosensitizers	A: HAL fluorescent cystoscopy with TURBT (n=86) B: White light cystoscopy with TURBT (n=82) All patients received single shot intravesical mitomycin, BCG for grade tumors or CIS

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Kriegmair, 2002[1] High	10 to 14 days, followup cystoscopy method not reported	Screened: Not reported Randomized: 165 (83 vs. 82) Post-randomization exclusions: None reported Lost to followup: 13 (6 vs. 7) Analyzed for recurrence (bladder cancer present): 101 (52 vs. 49)	Age (mean): 69 vs. 70 years Male: 82% vs. 70% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 4.6% vs. 6.2% CIS, 55% vs. 47% Ta, 18% vs. 20% T1, 7.7% vs. 16% T2 Grade: 32% vs. 12% G1, 32% vs. 42% G2, 9.2% vs. 12% G3	A vs. B Recurrence free at 10 to 14 days: 67% (35/52) vs. 46% (23/49), p<0.014 (per-protocol, patients with bladder cancer on initial cystoscopy); 62% (40/65) vs. 41% (26/64), p<0.031 (including patients without bladder cancer on initial cystoscopy or did not undergo repeat cystoscopy for other reasons)
Naselli, 2012[3] Italy Medium	1 year, followup with white light cystoscopy	Screened: 223 Randomized: 188 (95 vs. 93) Post-randomization exclusions: None reported Lost to followup: 7 (3 vs. 4) Analyzed for recurrence (Ta, T1, or CIS): 148 (76 vs. 72)	Age (mean): 71 vs. 72 years Male: 16% vs. 24% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 49% vs. 39% Stage: 76% vs. 72% Ta or CIS, 24% vs. 28% T1 Grade: 51% vs. 57% low, 49% vs. 43% high (including CIS)	A vs. B Recurrence at 3 months: 3.9% (3/76) vs. 17% (12/72), unadjusted RR 0.24 (95% CI 0.07 to 0.81), adjusted RR 0.26 (95% CI 0.07 to 0.75) Recurrence through 1 year: 32% (24/76) vs. 51% (37/72), unadjusted RR 0.62 (95% CI 0.41 to 0.92), adjusted RR 0.57 (95% CI 0.38 to 0.85); OR adjusted for age, year of enrollment, sex, clinical status, multifocal tumor, grading, staging and adjuvant therapy regimen
O'Brien, 2013[4] Medium	12 months, followup cystoscopy method not reported	Screened: Not reported Randomized: 249 (129 vs. 129) Post-randomization exclusions: None reported Lost to followup: 6 (3 vs. 3) Analyzed for recurrence (Ta or T1): 168 (86 vs. 82)	Age (mean): 68 vs. 68 years Male: 74% vs. 73% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 0% Stage and grade: 57% vs. 50% G1pTa or G2 (low grade) pTa/pT1; 17% vs. 13% G2 (high grade) pTa or G3pTa; 25% vs. 36% G2 (high grade) pTa or G3pT1; 14% vs. 26% secondary CIS	A vs. B Recurrence at 3 months: 20% (17/86) vs. 17% (14/82), p=0.7 Recurrence at 3 months, low-grade: 19% (9/48) vs. 9% (4/46) Recurrence at 3 months, high-grade: 21% (8/38) vs. 28% (10/36) Recurrence at 3 months, unifocal: 15% (8/52) vs. 17% (10/60) Recurrence at 3 months, multifocal: 26% (9/34) vs. 18% (4/22) Recurrence through 12 months: 31% (27/86) vs. 35% (29/82); adjusted HR 0.72 (P=0.36) (adjusted for age, focality, tumor grade and stage and postoperative mitomycin c) Recurrence through 12 months, low-grade: 15/48 (31%) vs. 13/46 (28%) Recurrence through 12 months, high-grade: 12/38 (32%) vs. 16/36 (44%) Recurrence through 12 months, unifocal: 13/52 (25%) vs. 20/60 (33%)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Kriegmair, 2002[1] High	Not reported	Not reported	
Naselli, 2012[3] Italy Medium	A vs. B False-positive findings: 21% (26/124) vs. 28% (46/164), RR 0.75 (95% CI 0.47 to 1.2)	None	
O'Brien, 2013[4] Medium	"No adverse reactions to HAL"	Guy's and St Thomas' Hospitals	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Riedl, 2001[181] (also Daniltchenko, 2005[182]) Medium	Germany Two centers 1998-2000	Patients with superficial bladder cancer	Muscle invasive bladder cancer	A: 5-ALA fluorescent cystoscopy with TURBT (n=51) B: White light cystoscopy with TURBT (n=51) Mitomycin for pTa and pT1G1-2, BCG for pT1G3, CIS, and failed mitomycin
Schumacher, 2010[183] Medium	Sweden Multicenter 2002-2005	Patients >19 years of age with suspected NMIBC (primary or recurrent) based on at least one cystoscopy	WHO general health status score >2 (Eastern Cooperative Oncology Group), porphyria or hypersensitivity to porphyrins, renal and/or hepatic impairment, malignancies other than basalioma, planned or existing pregnancy, or simultaneous participation in other trials	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=141) B: White light cystoscopy with TURBT (n=138) Patients received BCG for CIS, pTaG3, and pT1G2-3 starting 4 weeks after TURBT

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Riedl, 2001[181] (also Daniltchenko, 2005[Daniltchenko, 2005 Medium	60 months (median 42 vs. 39 months), followup ALA fluorescent cystoscopy at 6 weeks	Screened: Not reported Randomized: 115 Lost to followup: None reported Analyzed for recurrence (NMIBC): 102 (51 vs. 51)	Age (mean): 70 vs. 67 years Male: 71% vs. 73% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 78% vs. 78% Ta, 22% vs. 22% T1 Grade: 18% vs. 14% G1, 69% vs. 76% G2, 14% vs. 9.8% G3	A vs. B Residual tumor at 6 weeks: 16% (8/51) vs. 41% (21/51), p=0.003) Recurrence, through end of followup: 59% (30/51) vs. 75% (38/51) Median time to first recurrence (months): 12 vs. 5, p=0.015 Progression: 7.8% (4/51) vs. 18% (9/51), p=0.04 Secondary transurethral resections (per year): 0.92 vs. 1.17
Schumacher, 2010[183] Medium	12 months, followup with white light cystoscopy	Screened: Not reported Randomized: 300 (153 vs. 147) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 279 (141 vs. 138)	Age (mean): 70 vs. 69 years Male: 73% vs. 75% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 52% vs. 50% Stage and grade: 0.7% vs. 4.3% CIS, 55% vs. 48% pTaG1-2, 12% vs. 10% pTaG3 or pT1G1-2, 4.3% vs. 5.1% pT1G3, 0.7% vs. 3.6% pT2	A vs. B Recurrence-free at 12 months (n=141 and 138): 55% vs. 56% for all patients (p=0.69, log-rank test), 50% vs. 53% for patients with histologically verified tumor (n=119 and 119) on initial TURBT (p=0.98, log-rank test) Recurrence-free at 12 months, low risk tumor (n=68 and 76): 49% vs. 50% (p=0.51, log-rank test) Recurrence-free at 12 months, high risk tumor (n=51 and 43): 53% vs. 58% (p=0.35, log-rank test) Progression free at 12 months (n=136 and 130): 91% vs. 89% (p=0.11, log-rank test) Mortality: 3.5% (5/141) v. 2.9% (4/138)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Riedl, 2001[181] (also Daniltchenko, 2005[Daniltchenko, 2005 Medium	Not reported	Not reported	
Schumacher, 2010[183] Medium	A vs. B Adverse events: 28% vs. 18% Renal and genitourinary adverse events: 13% vs. 10%	Meda GmbH	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Stenzl, 2010[184] (also Grossman 2012[185]) US, Canada, and Europe RCT High	USA, Canada, and Europe Multicenter Study years not reported	Patients with suspected Ta or T1 bladder cancer, at increased risk for recurrence based on presence of multifocal tumors or recurrence within 12 months	Gross hematuria, porphyria, received BCG or multiple instillation chemotherapy in the 3 months before initial TURBT	A: White light cystoscopy following instillation of HAL, followed by second randomization: a: Fluorescent cystoscopy and TURBT (n=271) b: TURBT without fluorescent cystoscopy (excluded from recurrence analysis, n unclear) B: White light cystoscopy and TURBT (n=280) Intravesical BCG for high grade T1 or CIS

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Stenzl, 2010[184] (also Grossman 2012[185]) US, Canada, and Europe RCT High	9 months, followup with white light cystoscopy	Screened: 814 Randomized: 779 (395 vs. 384) Post-randomization exclusions: Unclear (some patients in HAL arm randomized out of study per protocol) Lost to followup: Unclear, 149 (71 vs. 78) did not complete study per protocol Analyzed for recurrence (Ta or T1): 551 (271 vs. 280)	Age (mean): 68 vs. 70 years Male: 78% vs. 79% White race: 92% vs. 96% Smoker: Not reported Recurrent bladder cancer: 63% vs. 56% Stage: 72% vs. not reported Ta, 17% vs. not reported T1, 11% vs. not reported CIS Grade: Not reported	A vs. B Recurrence through 9 months: 47% (128/271) vs. 56% (157/280) (p=0.03, log-rank test; ITT, includes 45 and 55 imputed recurrences due to lack of histological confirmation or lack of followup); 36% (72/200) vs. 46% (92/202) (p=0.03, log-rank test, per-protocol analysis) Recurrence through 9 months, initial cancer: 42% (42/101) vs. 49% (60/123), p=0.31 Recurrence through 9 months, recurrent cancer: 51% (86/170) vs. 62% (97/157), p=0.04 Recurrence through 9 months, TaG1 or TaG2: 45% (99/218) vs. 55% (113/204), p=0.02 Recurrence through 9 months, TaG3, Ta + CIS, T1, T1 + CIS: 55% (40/73) vs. 57% (47/83), p=0.48 Progression to muscle invasion through 9 months: 1.8% (5/271) vs. 1.8% (5/280) Recurrence-free through long-term followup (median 53 vs. 55 months): 38% (97/255) vs. 32% (83/261), p=0.14 Median time to recurrence: 16 vs. 9.4 months (p=0.04) Progression to muscle invasion through long-term followup: 2.4% (6/255) vs. 6.1% (16/261), p=0.16 Cystectomy through long-term followup: 4.8% (13/271) vs. 7.9% (22/280), p=0.16

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Stenzl, 2010[184] (also Grossman 2012[185]) US, Canada, and Europe RCT High	A vs. B Mortality: 1.4% (5/365) vs. 1.4% (5/361) at 9 months, 14% (39/271) vs. 16% (44/280) at median 53 to 55 months Bladder cancer mortality at long-term followup: 2.2% (6/271) vs. 2.9% (8/280) known bladder cancer deaths; 7.0% (19/271) vs. 8.6% (24/280) assuming deaths with incomplete information due to bladder cancer Any adverse event: 48% (202/365) vs. 51% (193/361) Renal or urinary adverse event: 31% vs. 32% Serious adverse event: 9.3% (39/365) vs. 8.4% (32/361) False-positives: 10% (91/933) vs. 12% (120/988)	Photocure ASA	

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Stenzl, 2011[186] Medium	Italy Two centers 2009-2010	Patients >19 years of age with suspected NMIBC based on at least 1 imaging procedure	WHO general health status score >2 (Eastern Cooperative Oncology Group), porphyria or hypersensitivity to porphyrins, renal and/or hepatic impairment, malignancies other than basalioma, planned or existing pregnancy, or simultaneous participation in other trials, or mental disorders	A: White light and fluorescent cystoscopy with TURBT following instillation of 5-ALA (n=183) B: White light and fluorescent cystoscopy with TURBT following instillation of placebo (n=176) CIS, pTaG3, or pT1G2-3 received BCG 4 weeks after TURBT

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Duration of Followup and Cystoscopic Followup Method	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results (report n/N when possible)
Stenzl, 2011[186] Medium	12 months, followup with white light cystoscopy	Screened: Not reported Randomized: 381 (192 vs. 189) Post-randomization exclusions: 11 (5 vs. 6) Lost to followup: None reported Analyzed for recurrence (NMIBC): 370 (183 vs. 176)	Age (mean): 66 years (overall) Male: 72% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage and grade: 33% vs. 28% pTaG1, 19% vs. 20% pTaG2, 1.1% vs. 0% pTaG3, 1.1% vs. 0.6% pT1G1, 8.7% vs. 8.5% pT1G2, 10% vs. 31% pT1G3, 5.5% vs. 4.5% pT2, 1.6% vs. 1.7% isolated CIS	A vs. B Recurrent tumor at 2 to 4 weeks, pTaG2-3 or T2 (with no indication for cystectomy): 65% (24/37) vs. 47% (17/36) Recurrence-free at 12 months (n=183 and 176): 64% vs. 73% (p=0.22); similar results in analyses stratified by high vs. low risk tumor, study center Progression-free at 12 months (n=183 and 176): 89% vs. 89% (p=0.91) Arm A (5-ALA), fluorescence cystoscopy vs. standard cystoscopy, detection rates CIS: 100% (49/49) vs. 65% (32/49) pTaG1: 96% (112/117) vs. 84% (98/117) pTaG2: 91% (64/70) vs. 81% (57/70) pTaG3: 100% (2/2) vs. 100% (2/2) pT1G1: 50% (1/2) vs. 50% (1/2) pT1G2: 86% (19/22) vs. 96% (21/22)

Appendix E6. Key Question 6: Included Randomized Controlled Trials

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Stenzl, 2011[186] Medium	A vs. B Adverse events: 33% (60/183) vs. 34% (60/176) Serious adverse events: 2.2% (4/183) vs. 1.1% (2/176) Fatal adverse events: 1.1% (2/183) vs. 1.1% (2/176)	Medac GmbH	

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Key Question	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Chahal, 2001[5] UK		Yes	Yes	Yes	Yes	Yes	No
Feil, 2003[6] Germany		Yes	Yes	Yes	No	Unclear	Yes
Friedrich, 2002[7] Germany	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Giannopoulos, 2001[8] Greece		Unclear	Yes	Yes	Yes	Unclear	No
Gibanel, 2002[9] Spain	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	No
Grossman, 2005[10] United States Lotan, 2009[11]	1, 5, 7	Yes	Yes	Yes	No	Yes	Yes
Grossman, 2006[12] United States	1, 5, 7	Yes	Yes	Yes	Yes	Yes	Yes
Gudjonsson, 2008[13] Sweden	1, 5, 7	Unclear	Yes	Yes	Yes	Yes	Yes
Gupta, 2009[14] India	1, 5, 7	Yes	Yes	No	Yes	Yes	Yes
Gutierrez Banos, 2001[15] Spain	1, 5, 7	Unclear	Yes	No	Yes	Yes	Yes
Halling, 2002[16] USA	1, 5, 7	Unclear	Yes	Yes	Unclear	Unclear	Yes
Ianari, 1997[17] Italy	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Irani, 1999[18] France	1, 5, 7	Unclear	Yes	Yes	Yes	Yes	Yes
Karnwal, 2010[19] USA	1, 5, 7	Yes	Yes	Yes	Yes	Yes	Unclear

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Moderate, High)
Chahal, 2001[5] UK	Yes	Yes	Yes	Yes	Moderate
Feil, 2003[6] Germany	Unclear	Yes	Yes	No	Moderate
Friedrich, 2002[7] Germany	Unclear	Yes	Yes	Yes	Moderate
Giannopoulos, 2001[8] Greece	Unclear	Yes	Yes	Yes	Moderate
Gibanel, 2002[9] Spain	Unclear	Yes	Yes	Yes	Moderate
Grossman, 2005[10] United States Lotan, 2009[L	Yes	Yes	Yes	Yes	Low
Grossman, 2006[12] United States	Yes	Yes	Yes	Yes	Low
Gudjonsson, 2008[13]	Unclear	Yes	Yes	Yes	Moderate
Gupta, 2009[14] India	Yes	Yes	Yes	Yes	Moderate
Gutierrez Banos, 2001[15] Spain	Unclear	Yes	Yes	Yes	Moderate
Halling, 2002[16] USA	Unclear	Yes	Yes	No	High
Ianari, 1997[17] Italy	Unclear	Yes	Yes	Yes	Moderate
Irani, 1999[18] France	Unclear	Yes	Yes	Yes	Moderate
Karnwal, 2010[19] USA	Unclear	Yes	Yes	Yes	Moderate

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Key Question	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Leyh, 1997 Germany, UK, and France	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Leyh, 1997 Germany and France	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Lodde, 2003 Italy	1, 5, 7	Yes	Yes	Yes	No	Unclear	Yes
Messing, 2005 USA	1, 5, 7	Unclear	Yes	Yes	No	Yes	Yes
Mian, 1999 Italy	1, 5, 7	Yes	Yes	Yes	No	Unclear	Yes
Mian, 2000 Italy and Austria	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Nasuti, 1999 USA	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
O'Sullivan, 2012 New Zealand	1, 5, 7	Yes	Yes	No	Yes	Unclear	Unclear
Paoluzzi, 1999 Italy	1, 5, 7	Unclear	Yes	Yes	Unclear	Unclear	Yes
Pfister, 2003 France	1, 5, 7	Yes	Yes	Yes	Yes	Unclear	Yes
Placer, 2002 Spain	1, 5, 7	Yes	Yes	Yes	No	Unclear	Yes
Pode, 1999 Israel	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Ponsky, 2001 USA	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Quek, 2002 Singapore	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Raitanen, 2001 Finland	1, 5, 7	Yes	Yes	Yes	Yes	Unclear	Yes
Saad, 2002 UK	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Sanchez-Carbayo, 2001 Spain	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Sarosdy, 2002 USA	1, 5, 7	Unclear	Yes	Yes	Yes	Yes	Yes
Sawczuk, 2000 USA	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Moderate, High)
Leyh, 1997[20] Germany, UK, and France	Yes	Yes	Yes	Yes	Moderate
Leyh, 1997[21] Germany and France	Yes	Yes	Yes	Yes	Moderate
Lodde, 2003[22] Italy	Unclear	Yes	Yes	Yes	Moderate
Messing, 2005[23] USA	Unclear	Yes	Yes	Yes	Moderate
Mian, 1999[24] Italy	Unclear	Yes	Yes	Yes	Moderate
Mian, 2000[25] Italy and Austria	Unclear	Yes	Yes	Yes	Moderate
Nasuti, 1999[26] USA	Unclear	Yes	Yes	Yes	Moderate
O'Sullivan, 2012[27] New Zealand	Unclear	Yes	Yes	Yes	Moderate
Paoluzzi, 1999[28] Italy	Unclear	Yes	Yes	Yes	Moderate
Pfister, 2003[29] France	Yes	Yes	Yes	Yes	Moderate
Placer, 2002[30] Spain	Unclear	Yes	Yes	Yes	Moderate
Pode, 1999[31] Israel	Unclear	Yes	Yes	Yes	Moderate
Ponsky, 2001[32] USA	Yes	Yes	Yes	Yes	Moderate
Quek, 2002[33] Singapore	Unclear	Yes	Yes	Yes	Moderate
Raitanen, 2001[34] Finland	Unclear	Yes	Yes	No	Moderate
Saad, 2002[35] UK	Unclear	Yes	Yes	Yes	Moderate
Sanchez-Carbayo, 2001[36] Spain	Unclear	Yes	Yes	Yes	Moderate
Sarosdy, 2002[37] USA	Yes	Yes	Yes	Yes	Moderate
Sawczuk, 2000[38] USA	Unclear	Yes	Yes	Yes	Moderate

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Key Question	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Schamhart, 1998[39] the Netherlands	1, 5, 7	Unclear	Yes	Yes	Yes	Yes	Yes
Serretta, 1998[40] Italy	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Shariat, 2006[41] USA, Europe, Japan, Canada	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Sharma, 1999[42] USA	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Thomas, 1999[43] Europe	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[44] UK	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
van Der Poel, 1998[45] the Netherlands	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Varella-Garcia, 2004[46]	1, 5, 7	Unclear	Yes	Yes	Yes	Yes	Yes
Witjes, 1998[47] the Netherlands	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes
Zippe, 1999[48] USA	1, 5, 7	Unclear	Yes	Yes	Yes	Unclear	Yes

Appendix F1. Quality Assessment of Biomarker Studies

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Moderate, High)
Schamhart, 1998[39] the Netherlands	Unclear	Yes	Yes	No	Moderate
Serretta, 1998[40] Italy	Unclear	Yes	Yes	Yes	Moderate
Shariat, 2006[41] USA, Europe, Japan, Canada	Unclear	Yes	Yes	Yes	Moderate
Sharma, 1999[42] USA	Unclear	Yes	Yes	Yes	Moderate
Thomas, 1999[43] Europe	Unclear	Yes	Yes	Yes	Moderate
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997[44] UK	Unclear	Yes	Yes	Yes	Moderate
van Der Poel, 1998[45] the Netherlands	Unclear	Yes	Yes	Yes	Moderate
Varella-Garcia, 2004[46]	Yes	Yes	Yes	Yes	Moderate
Witjes, 1998[47] the Netherlands	Unclear	Yes	Yes	Yes	Moderate
Zippe, 1999[48] USA	Yes	Yes	Yes	Yes	Moderate

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Addeo, 2010[93]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1987[49] Study One (followup of Niijima, 1983)	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1987[49] Study Two	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1992[51]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1997[52] (Brit J Urol)	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1997[53] (J Urol)	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1999[53]	3	Unclear	Unclear	No: differences in single vs multiple tumors	Yes	Unclear	Unclear
Au, 2001[149]	3	Unclear	Yes	Yes	Yes	Unclear	No
Babjuk, 2005[172]	6	Unclear	Unclear	Yes	Yes	No	No
Berrum-Svennung, 2008[54]	3	Yes	Unclear	Yes	Yes	Yes	No
Bilen, 2000[95]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Boccardo, 1994[96]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Böhle, 2009[55]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Bouffioux, 1995[150]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Cai, 2008[97]	3	Unclear	Yes	Yes	Yes	Unclear: double blind; statician masked	Unclear: double blind
Cheng, 2005[187] (Clin Urol)	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Addeo, 2010[93]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Akaza, 1987[49] Study One (followup of Niijima, 1983)	Unclear	Yes	Overall: Yes Differential: No	Yes	Unclear	Yes	Medium
Akaza, 1987[49] Study Two	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Akaza, 1992[51]	Unclear	Yes	Overall: No Differential: No	Yes	Unclear	Yes	High
Ali-El-Dein, 1997 (Brit J Urol)	Unclear	No	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Ali-El-Dein, 1997 (J Urol)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Ali-El-Dein, 1999[53]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes: 11% not available for evaluation for reasons not reported	Unclear	High
Au, 2001[149]	No	Yes	Overall: Yes Differential: Yes	No	Yes	Yes	Medium
Babjuk, 2005[172]	No	No	Unclear	Yes	No	Yes	High
Berrum-Svennung, 2008[54]	Yes	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Bilen, 2000[95]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Boccardo, 1994[96]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Böhle, 2009[55]	Unclear	Yes	Overall: Yes Differential: No	Yes	Yes	Yes	Medium
Bouffioux, 1995[150]	Unclear	Yes	Overall: No Differential: Unclear	Yes	Yes	Yes	Medium
Cai, 2008[97]	Unclear: double blind	Yes	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium
Cheng, 2005[187] (Clin Urol)	Unclear	No	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Cheng, 2005[56] (Int. Journal of Urol.)	3	Unclear	Unclear	Some differences in distribution of tumor grade	Yes	Unclear	Unclear
Cho, 2009[98]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
De Nunzio, 2011[57]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
De Reijke, 2005[99]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
DeBruyne, 1988[101] Witjes, 1998a DeBruye, 1992	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Di Lorenzo, 2010[103]	3	Yes	Yes	Yes	Yes	No	No
Di Stasi, 2003[104]	3	Yes	Yes	Yes	Yes	Unclear	Unclear
Dragoescu, 2011[173]	6	Unclear	Unclear	Yes	Yes	No	No
Ducheck, 2010[105] Hemdan, 2014[106]	3	Yes	Yes	Yes	Yes	Unclear	Unclear
Ersoy, 2013[58]	3	No	Unclear	No	Yes	Unclear	Unclear
Eto, 1994[107]	3	Unclear	Yes	Yes (except age)	Yes	Unclear	Unclear
Flamm, 1990[151]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Filbeck, 2002[174] Burger, 2008[188] Denginger, 2007[176] Denzinger, 2007b	6	Unclear	Unclear	No	Yes	No	No
Denzinger, 2007[175]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Friedrich, 2007[108]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Geavlete, 2010[177, 178]	6	Unclear	Yes	Yes	Yes	Yes	No
Geavlete, 2011	6	Unclear	Yes	Yes	Yes	Yes	No
Giannakopoulos, 1998[2]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Cheng, 2005[56] (Int. Journal of Urol.)	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Cho, 2009[98]	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
De Nunzio, 2011[57]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
De Reijke, 2005[99]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
DeBruyne, 1988[101] Witjes, 1998a DeBruye, 1992	Unclear	Yes	Overall: No Differential: Yes	Yes	No	Yes	Medium
Di Lorenzo, 2010[103]	No	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Di Stasi, 2003[104]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Dragoescu, 2011[173]	No	Yes	Yes	Yes	No	Yes	Medium
Ducheck, 2010[105] Hemdan, 2014[106]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Ersoy, 2013[58]	Unclear	No	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	High
Eto, 1994[107]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Flamm, 1990[151]	Unclear	No	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Filbeck, 2002[174] Burger, 2008[188] Denginger, 2007[176] Denzinger, 2007b	No	Yes	Yes	Yes	No	Yes	Medium
Denzinger, 2007[175]	Unclear	No	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Friedrich, 2007[108]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Geavlete, 2010[177, 178]	No	Yes	Yes	Yes	No	Yes	Medium
Geavlete, 2011	No	Yes	Yes	Yes	No	Yes	Medium
Giannakopoulos, 1998[2]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Giannopoulos, 2003[109]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Gontero, 2013[110]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Gruenwald, 1997[152]	3	Yes	Unclear	Yes	Yes	Unclear	Unclear
Gudjónsson, 2009[59]	3	Unclear	No	Yes	Yes	Unclear	Unclear
Gulpinar, 2012[111]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Gustafson, 1991[60]	3	Unclear	Unclear	Yes	No	Unclear	Unclear
Harland, 2007[170]	4	Unclear	No	Yes	Yes	Unclear	No
Hendricksen, 2008[153, 179]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hermann, 2011[179]	6	Unclear	Unclear	Yes	Yes	No	No
Herr, 1995[62] Herr, 1988[61] Herr, 1997[64] Cookson, 1997[63] Pinsky, 1985	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hinotsu, 2006[113]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hinotsu, 2011[112]	3	Yes (minimization method)	Yes (minimization method)	Yes	Yes	Unclear	Unclear
Hirao, 1992[66]	3	Unclear	Unclear	No (grade)	Yes	Unclear	Unclear
Hoeltl, 1991[154]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Huland, 1990[114]	3	Unclear	Unclear	No (age, grade)	Yes	Unclear	Unclear
Igawa, 1996[67]	3	Unclear	Unclear	Unclear	No	Unclear	Unclear
Irie, 2003[155]	3	No (sequential)	No	Yes	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Giannopoulos, 2003[109]	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Gontero, 2013[110]	Unclear	Yes	Overall: Yes Differential: Yes	No; analyzed all individual who completed maintenance course for QOL	Yes	Yes	High
Gruenwald, 1997[152]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Gudjónsson, 2009[59]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Gulpinar, 2012[111]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Gustafson, 1991[60]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Harland, 2007[170]	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Hendricksen, 2008[153, 179]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Hermann, 2011[179]	No	Yes	Yes	Yes	Yes	Yes	Medium
Herr, 1995[62] Herr, 1988[61] Herr, 1997[64] Cookson, 1997[63] Pinsky, 1985	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Hinotsu, 2006[113]	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Hinotsu, 2011[112]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Hirao, 1992[66]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Hoeltl, 1991[154]	Unclear	Yes	Overall: No Differential: Unclear	Yes	Yes	Yes	Medium
Huland, 1990[114]	No	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Igawa, 1996[67]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Irie, 2003[155]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Low

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Jarvinen, 2012[139] Rintala, 1996[140] Rintala, 1995[138]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Jimenez-Cruz, 1997[115]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kaasinen, 2000[116]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kaasinen, 2003[117]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Karaolides, 2012[180]	6	Unclear	Unclear	Yes	Yes	No	No
Koga, 2004[156]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Koga, 2010[68]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Koontz, 1981[69] (prophylaxis)	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Koontz, 1981[69] (treatment)	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Krege, 1996[70]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kriegmair, 2002[1]	6	Unclear	Unclear	Yes	Yes	No	No
Kuroda, 2004[157]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Kurth, 1997[71] Kurth, 1984[72]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lamm, 1991[118]	3	Yes	Yes	Yes	Yes	Unclear	Unclear
Lamm, 1995[119]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lamm, 2000[73] Lerner, 2007[74]	3	Unclear	Unclear	Yes, although specific grade and stage of tumor not reported by group	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Jarvinen, 2012[139] Rintala, 1996[140] Rintala, 1995[138]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Jimenez-Cruz, 1997[115]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No, could not get INF for 12 patients	Yes	Medium
Kaasinen, 2000[116]	Unclear	Yes	Overall: Yes Differential: Yes	No 13% not eligible for randomization violations	Yes	Yes	Medium
Kaasinen, 2003[117]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Karaolides, 2012[180]	No	Yes	Yes	Yes	No	Yes	Medium
Koga, 2004[156]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Koga, 2010[68]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Koontz, 1981[69] (prophylaxis)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Koontz, 1981[69] (treatment)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Krege, 1996[70]	Unclear	All but 1 patient analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Kriegmair, 2002[1]	No	Yes	No	Yes	No	Yes	High
Kuroda, 2004[157]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
Kurth, 1997[71] Kurth, 1984[72]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Lamm, 1991[118]	Unclear	all analyzed	Overall: Yes Differential: Yes	No 9% randomized not eligible and not analyzed	No	Yes	Medium
Lamm, 1995[119]	Unclear	Yes	Overall: Yes Differential: Unclear as 16% not evaluable but	Yes	No: 4.7% found ineligible after randomization	Yes	Medium
Lamm, 2000[73] Lerner, 2007[74]	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Liu, 2006[120]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lundholm, 1996[121] Malmstrom, 1999[122] Gardmark, 2007[123]	3	Unclear	Yes	Unclear as only tumor information provided which showed no differences	Yes	Unclear	Unclear
Malmström, 2002[124]	3	Unclear	Unclear	Yes	Yes	Yes	Unclear
Mangiarotti, 2008[125]	3	Unclear	Unclear	Yes	No	Unclear	Unclear
Martinez-Pineiro, 1990[126]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Martinez-Pineiro, 2002[158]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Martinez-Pineiro, 2005[159]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Masters, 1999[160]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Matsumura, 1992[75]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1990[76]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1992[77]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1993[78]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1996[127]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Mitsumori, 2004[161]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Liu, 2006[120]	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Lundholm, 1996[121] Malmstrom, 1999[122] Gardmark, 2007[123]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Malmström, 2002[124]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Mangiarotti, 2008[125]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Martinez-Pineiro, 1990[126]	Unclear	Yes	Overall: Yes Differential: Unclear	No, excluded patients lost to followup	No	Unclear	Medium
Martinez-Pineiro, 2002[158]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Martinez-Pineiro, 2005[159]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Masters, 1999[160]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Matsumura, 1992[75]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Unclear	Medium
Melekos, 1990[76]	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium
Melekos, 1992[77]	Unclear	No	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Melekos, 1993[78]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes: 15% excluded due to protocol violation, loss to followup, or	Yes	Medium
Melekos, 1996[127]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Mitsumori, 2004[161]	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Mohsen, 2010[128]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Morales, 1992[162]	3	No (sequential)	No	Unclear	Yes	Unclear	Unclear
Naselli, 2012[3]	6	Yes	Unclear	Yes	Yes	No (pathologist blinded but followup cystoscopies not)	No
Nepple, 2010[129]	3	Yes	Yes	Baseline characteristics by group not reported	Yes	Unclear	Unclear
Niijima, 1983[50] Akaza,1987[49]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Nomata, 2002[163]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Obata, 1994[79]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
O'Brien, 2013[4]	6	Unclear	Yes	Yes	Yes	No	No
Oddens, 2013[164]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ojea, 2007[130]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Okamura, 2002[80]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Oosterlinck, 1993[81]	3	Unclear	Unclear	No (grade) Unclear (age, sex)	Yes	Unclear	Unclear
Ossterlinck, 2011[131]	3	Unclear	Unclear	No: gender and performance status differences	Yes	Unclear	Unclear
Pagano, 1991[82] Pagano, 1990[83]	3	Unclear	Unclear	Unclear, baseline characteristics not given	Yes	Unclear	Unclear
Pagano, 1995 Bassi, 1992[133]	3	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Palou, 2001[84]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Papatsoris, 2004[189]	3	No	Unclear	Yes	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Mohsen, 2010[128]	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Morales, 1992[162]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Low
Naselli, 2012[3]	No	Yes	Yes	Yes	No	Yes	Medium
Nepple, 2010[129]	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Niijima, 1983[50] Akaza,1987[49]	Unclear	Yes	Overall: Yes Differential: No	Yes	Unclear	Yes	Medium
Nomata, 2002[163]	Unclear	Yes	Overall: No Differential: Yes	Yes	Yes	Yes	Medium
Obata, 1994[79]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
O'Brien, 2013[4]	No	Yes	Yes	Yes	No	Yes	Medium
Oddens, 2013[164]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Ojea, 2007[130]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Okamura, 2002[80]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Oosterlinck, 1993[81]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Ossterlinck, 2011[131]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Pagano, 1991[82] Pagano, 1990[83]	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	High
Pagano, 1995 Bassi, 1992[133]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Low
Palou, 2001[84]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Papatsoris, 2004[189]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	High

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Porena, 2010[134]	3	Yes	Unclear	Yes	Yes	No	No
Portillo, 1997[85]	3	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Rajala, 1999[86]	3	Unclear	Unclear	No (grade)	Yes	Yes	Unclear
Rajala, 2002[87]	3	Unclear	Unclear	Yes	Yes	No	No
Riedl, 2001[181] Daniltchenko, 2005[182]	6	Unclear	Unclear	Yes	Yes	No	No
Rintala, 1991[136] Jarvinen, 2009[137]	3	No, based on date of birth	Unclear	No, difference in recurrence rate before therapy	Yes	Unclear	Unclear
Rubben, 1988[141]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Saika, 2010[88]	3	Yes	Unclear	Yes	Yes	Unclear	Unclear
Schumacher, 2010[183]	6	Unclear	Yes	Yes	Yes	Yes	No
Schwaibold, 1997[166]	3	Unclear	Unclear	No	Yes	Unclear	Unclear
Sengiku, 2013[142]	3	Yes	Yes	Yes	Yes	Unclear	Unclear
Serretta, 2010[167]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Shuin, 1994[143]	3	Unclear	Unclear	Yes	No	Unclear	Unclear
Solsona, 1999[89]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Stavropoulos, 2002[90]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Stenzl, 2010[184] Grossman, 2012[185] Mostafid, 2009[190]	6	Unclear	Unclear	Yes	Yes	No (pathologist blinded but followup cystoscopies not)	No

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Porena, 2010[134]	No	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Portillo, 1997[85]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Rajala, 1999[86]	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Rajala, 2002[87]	No	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Riedl, 2001[181] Daniltchenko, 2005[182]	No	Yes	Yes	Yes	No	Yes	Medium
Rintala, 1991[136] Jarvinen, 2009[137]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Rubben, 1988[141]	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
Saika, 2010[88]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Schumacher, 2010[183]	No	Yes	No	Yes	No	Yes	Medium
Schwaibold, 1997[166]	Unclear	Yes	Overall: No Differential: No	Yes	Yes	Yes	Medium
Sengiku, 2013[142]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Serretta, 2010[167]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Shuin, 1994[143]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Unclear	High
Solsona, 1999[89]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Stavropoulos, 2002[90]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Stenzl, 2010[184] Grossman, 2012[185] Mostafid, 2009[190]	No	Yes	No	Yes	No	Yes	High

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Key Question	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Stenzl, 2011[186] Penkoff, 2007[191]	6	Unclear	Unclear	Yes	Yes	Yes	Yes
Tolley, 1996[91] Tolley, 1988[92]	3	Yes	Yes	Yes	Yes	Unclear	Unclear
Turkeri, 2010[168]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ueda, 1992[169]	3	Unclear	Unclear	No	Yes	Unclear	Unclear
Van Der Meijden, 2001[144] Sylvester, 2010[145]	3	Unclear	Yes	Yes	Yes	Unclear	Unclear
Van Gils-Gielen, 1995[192]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Witjes, 1993[146] Witjes, 1996[147]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Witjes, 1998b[148]	3	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Appendix F2. Quality Assessment of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Stenzl, 2011[186] Penkoff, 2007[191]	Yes	Yes	No	Yes	No	Yes	Medium
Tolley, 1996[91] Tolley, 1988[92]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Turkeri, 2010[168]	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Ueda, 1992[169]	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Van Der Meijden, 2001[144] Sylvester, 2010[145]	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Van Gils-Gielen, 1995[192]	Unclear	Yes	Yes/Yes	Yes	No	Yes	Medium
Witjes, 1993[146] Witjes, 1996[147]	Unclear	Unclear	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Witjes, 1998b[148]	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium

Appendix F3. Bladder Cancer Quality Ratings of Cohort Studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?
Mulders, 1994[171]	Yes, all patients in registry	Yes	Yes	No	Not reported

Appendix F3. Bladder Cancer Quality Ratings of Cohort Studies

Author, Year	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Mulders, 1994[171]	Yes	No	No	Yes	High

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in 1) persons with signs or symptoms warranting evaluation for possible bladder cancer or 2) persons undergoing surveillance for previously treated bladder cancer?							
Quantitative NMP22: Sensitivity and specificity	15 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate
Qualitative NMP22: Sensitivity and specificity	4 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Qualitative BTA: Sensitivity and specificity	17 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Quantitative BTA: Sensitivity and specificity	3 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
FISH: Sensitivity and specificity	6 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Immunocyt: Sensitivity and specificity	4 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
CxBladder: Sensitivity and specificity	1 study of diagnostic accuracy	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Quantitative NMP22 versus qualitative BTA: Sensitivity and specificity	5 studies of diagnostic accuracy	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Other head-to-head urinary biomarkers	No studies						Insufficient
Various urinary biomarkers plus cytology versus the urinary biomarker alone: Sensitivity and specificity	10 studies of diagnostic accuracy	Moderate	Consistent	Direct	Precise	Not detected	Moderate

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
KQ1a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, ethnicity), or according to the nature of the presenting signs or symptoms?							
Effects of tumor stage: Sensitivity	Quantitative NMP22: 8 studies Qualitative BTA: 14 studies	Moderate	Consistent	Direct	Precise	Not detected	High
Effects of tumor grade: Sensitivity	Quantitative NMP22: 8 studies Qualitative BTA: 15 studies	Moderate	Consistent	Direct	Precise	Not detected	High
Effects of tumor size: Sensitivity	2 studies	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Effects of patient characteristics (age, sex, smoking status, and presence of other clinical conditions): sensitivity and specificity		Moderate	Consistent	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
2. For patients with non-muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., Guidelines of the European Association of Urology or based on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by an assessed risk-adapted approach?							
Mortality, recurrence, progression, need for cystectomy, quality of life	No studies	-	-	-	-	-	Insufficient

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
3. For patients with non-muscle-invasive bladder cancer treated with transurethral resection of bladder tumor (TURBT), what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?							
BCG vs. no intravesical therapy							
All-cause mortality	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Bladder caner-specific mortality	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Recurrence	5 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	6 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Mitomycin C vs. no intravesical therapy							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Recurrence	6 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin vs. no intravesical therapy							
All cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	8 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	5 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Epirubicin vs. no intravesical therapy							
Recurrence	9 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	8 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Low
Gemcitabine vs. no intravesical therapy							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Interferon-alpha vs. no intravesical therapy							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Interferon-gamma vs. no intravesical therapy							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Thiotepa vs. no intravesical therapy							
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?							
BCG versus mitomycin C							
All-cause mortality	7 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Bladder cancer- specific mortality	5 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Recurrence	9 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low
Progression	7 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
BCG vs. BCG plus mitomycin C given sequentially							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Bladder cancer- specific mortality	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Recurrence	4 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG plus MMC given sequentially vs. MMC							
All-cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer- specific mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
BVC vs. doxorubicin							
All-cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. epirubicin							
All-cause mortality	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	5 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate
Progression	5 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus epirubicin given sequentially							
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. Epirubicin plus interferon							
Bladder cancer-specific mortality	1 RCT						Low
Progression	1 RCT						Low
BCG vs. gemcitabine							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Recurrence	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
Progression	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Quality of life	1 RCT						Low
BCG vs. BCG plus gemcitabine given sequentially							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus epirubicin given sequentially							
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. interferon alpha-2a							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. alternating BCG and interferon alpha-2b							

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. coadministration of BCG and interferon alpha-2b							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. thiotepa							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. doxorubicin							
Recurrence	4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Inconsisent	Direct	Imprecise	Not detected	Low
MMC vs. epirubicin							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. gemcitabine							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
MMC vs. interferon-alpha							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Preogression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. interferon-gamma							
Recurrence	1 RCT						Low
Doxorubinc vs. epirubicin							
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. thiotepa							
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Epirubicin vs. interferon-alpha							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
b. Does the comparative effectiveness differ according to tumor characteristics, such as stage, grade, size, multiplicity, whether the tumor is primary or recurrent, or molecular/genetic markers?	Varied depending on tumor characteristic	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities?	No studies	-	-	-	-	-	Insufficient
d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?							
Standard vs. lower dose BCG: Recurrence, progression, mortality, adverse events	6 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Maintenance vs. induction BCG: Recurrence, progression, adverse events	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
BCG maintenance for 1 vs. 3 years: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin C single vs. 5 instillations: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin C induction vs. maintenance: Recurrence, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin C maintenance therapy with increased frequency and number of instillations vs. fewer instillations: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Mitomycin C optimized vs. nonoptimized administration: Recurrence, adverse events	2 RCTs	Moderate	Inconsisetnt	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Doxorubicin eight weeks vs. two years: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin induction vs. maintenance: Recurrence, progression, mortality, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin prior to vs. after TURBT: Recurrence, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Epirubicin higher vs. lower doses: recurrence, progression, adverse events	3 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Epirubicin single vs. multiple instillations: Recurrence, progression, bladder cancer mortality, adverse events	3 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Epirubicin maintenance vs. induction without maintenance: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Epirubicin more versus less intensive therapy: Recurrence, adverse events	5 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low
Thiotepa 30 vs. 60 mg: Recurrence, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Interferon alpha-2b, high vs. lower doses: recurrence, progression, resolution of bladder cancer marker lesions	3 RCTs				Imprecise		Low
MMC or doxorubicin on day of TURBT vs. 1 to 2 weeks after TURBT: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC or doxorubicin maintenance vs. no maintenance: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
4. For patients with high risk non-muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?							
Mortality, recurrence, progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
5. In surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?	No Studies	-	-	-	-	-	Insufficient
a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	No Studies	-	-	-	-	-	Insufficient
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?	No Studies	-	-	-	-	-	Insufficient

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
c. Does the comparative effectiveness differ according to the length of surveillance intervals?	No Studies	-	-	-	-	-	Insufficient
d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or ethnicity?	No Studies	-	-	-	-	-	Insufficient
6. For initial diagnosis or surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?							
Fluorescent cystoscopy vs. white light cystoscopy							
Mortality	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Recurrence	13 RCTs	Moderate	Inconsistent	Direct	Precise	Suspected	Low
Progression	6 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Narrow band imaging vs. white light cystoscopy							
Recurrence	1 RCT	Moderate	Cannot determine	Direcgt	Imprecise	Not detected	Low
7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?							
Urinary biomarkers: Adverse clinical outcomes	No Studies	-	-	-	-	-	Insufficient
Fluorescent vs. white light cystoscopy: False positives	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Fluorescent vs. white light cystoscopy: Renal and genitourinary adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
8. What are the comparative adverse effects of various treatments for non-muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?							
BCG vs. no intravesical therapy: Local and systemic adverse events	4 RCTs (harms only reported for BCG arm)	High	Inconsistent	Direct	Imprecise	Not detected	Low
Non-BCG intravesical therapies vs. no intravesical therapy: Local and systemic adverse events	Varied depending on intravesical agent	High	Inconsistent	Direct	Imprecise	Not detected	Low for local adverse events, insufficient for systemic adverse events
BCG vs. MMC							

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Local adverse events	2 to 6 RCTs	Moderate	Consistent	Direct	Imprecise (precise for cystitis and hematuria)	Not detected	Low (moderate for cystitis and hematuria)
Systemic adverse events	2 to 4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus MMC given sequentially							
Discontinuation of therapy	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG plus MMC given sequentially vs. MMC							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Discontinuation of therapy	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. doxorubicin							

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Local adverse events	1 to 3 RCTs	Moderate	Inconsistent or cannot determine	Direct	Imprecise	Not detected	Low (cystitis); insufficient (dysuria and hematuria)
BCG vs. epirubicin							
Local adverse events	1 to 4 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Discontiuation of therapy	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
Systemic adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus epirubicin given sequentially							
Local adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Discontinuation of therapy							

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
BCG vs. gemcitabine							
Local adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 to 2 RCTs	Moderate	Consistent or cannod determine	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus gemcitabine given sequentially							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. interferon alpha-2a							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. coadministration of BCG and interferon alpha-2b							
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. thiotepa							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin vs. doxorubicin							
Local advere events	4 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
Mitomycin vs. epirubicin							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin vs. interferon-alpha							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Mitomycin vs. gemcitabine							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. epirubicin							
Local adverse events	1 to 3 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. thiotepa							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Epirubicin vs. interferon-alpha							

Appendix G. Strength of Evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?	No studies	-	-	-	-	-	Insufficient

BCG=bacillus Calmette–Guérin, CI=confidence interval, IFN=interferon, MMC=mitomycin C, RR=relative risk, TURBT=transurethral resection of bladder tumor

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