Exact Search Strings

MEDLINE searches refined (performed 3/11/2005)

1. Search **("Erythropoietin"[MeSH] OR "Erythropoietin, Recombinant"[MeSH] OR "Epoetin Alfa"[MeSH] OR "epoetin beta"[Substance Name])**
2. Search **erythropoietin OR epoetin* OR epo OR eprex OR neorecormon OR aranesp OR procrit**
3. 1 OR 2
4. Search **"Neoplasms"[MeSH] OR "Carcinoma"[MeSH] OR malignan* OR cancer* OR oncolog* OR myelodysplas* OR tumor* OR tumour* OR neoplas* OR carcinom***
5. 3 AND 4
6. Search (**"Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trials"[MeSH]) OR "Random Allocation"[MeSH] OR "Double-Blind Method"[MeSH] OR "Single-Blind Method"[MeSH]**
7. Search **"Clinical Trial"[Publication Type] OR "Clinical Trials"[MeSH] OR "clinical trial"**
8. Search ((**singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*))**
9. Search **"Placebos"[MeSH] OR placebo* OR random***
10. Search **"Research Design"[MeSH:NoExp] OR "Comparative Study"[MeSH] OR "Evaluation Studies"[MeSH] OR "Follow-Up Studies"[MeSH]**
11. Search **"Prospective Studies"[MeSH] OR control* OR prospectiv* OR volunteer***
12. 6 OR 7 OR 8 OR 9 OR 10 OR 11
13. 5 AND 12
14. 13 AND PY=1998-2005 NOT (animals NOT humans)

15. Search **"darbepoetin alfa"[Substance Name] OR aranesp OR darbepoetin**
16. 15 AND 4
17. 16 AND 12

This set was not restricted

18. Search **"Epidemiologic Studies" [MeSH] OR "Incidence" [MeSH] OR predict* OR prognos* OR course* OR model* OR respon***
19. 5 AND 18
20. 16 AND 18
21. 19 OR 20
22. 21 AND PY=1998-2005 NOT (animals NOT humans)

EMBASE revised search (performed 4/7/2005)

1. **'erythropoietin'**/exp OR **'erythropoietin, recombinant'**/exp OR **'epoetin alfa'**/exp OR **'epoetin beta'**/exp AND [humans]/lim AND [1998-2005]/py
2. erythropoietin OR **epoetin*** OR **eprex** OR **neocormon** OR **aranesp** OR **procrit** OR **darbepoetin*** AND [humans]/lim AND [1998-2005]/py
3. deleted
4. **'neoplasms'**/exp OR **'carcinoma'**/exp AND [humans]/lim AND [1998-2005]/py
5. **malignan*** OR **cancer*** OR **oncolog*** OR **myelodysplas*** OR **tumor*** OR **tumour*** OR **neoplas*** OR **carcinoma*** AND [humans]/lim AND [1998-2005]/py
6. #1 OR #2
7. #4 OR #5
8. #6 AND #7
9. **'clinical trial'**:it OR **'randomized controlled trial'**:it AND [1998-2005]/py
10. **'randomized controlled trials'**/exp OR **'random allocation'**/exp OR **'double-blind method'**/exp OR **'single-blind method'**/exp OR **'clinical trials'**/exp OR **'research design'**/exp OR **'placebos'**/exp AND [humans]/lim AND [1998-2005]/py
11. deleted
12. (**singl*** OR **doubl*** OR **trebl*** OR **tripl***) AND (**mask*** OR **blind***) AND [humans]/lim AND [1998-2005]/py
13. **placebo*** OR **random*** OR **control*** OR **prospectiv*** OR **volunteer*** AND [humans]/lim AND [1998-2005]/py
14. **'comparative study'**/exp OR **'evaluation studies'**/exp OR **'follow-up studies'**/exp OR **'prospective studies'**/exp AND [humans]/lim AND [1998-2005]/py
15. #9 OR #10 OR #12 OR #13 OR #14
16. #8 AND #15
17. #16/EMBASE

18. **'epidemiologic studies'**/exp OR **'incidence'**/exp AND [humans]/lim AND [1998-2005]/py
19. **predict*** OR **prognos*** OR **course*** OR **model*** OR **respon*** AND [humans]/lim AND [1998-2005]/py
20. #18 OR #19
21. #8 AND #20
22. #21/EMBASE

KQ1 Sample Data Abstraction Forms

I. Study Eligibility

first author, year:

Reviewer:

TYPE OF STUDY 1. Is the study described as randomised? NB: Answer 'no' if the study is in cross over or quasi randomised design	Yes OR Unclear Go to Next question No **Exclude**
PARTICIPANTS IN THE STUDY 2. Did the participants in the study have a previous treated or untreated malignant disease?	Yes OR Unclear Go to Next question No **Exclude**
3. Were the participants anaemic or at risk for anaemia from chemotherapy and/or radiotherapy or their malignant disease?	Yes OR Unclear Go to Next question No **Exclude**
INTERVENTIONS IN THE STUDY 4. Was one group given Epoetin alfa or Epoetin beta subcutaneously or intravenously (not orally) in a dose of at least 300U /kg /week for at least four weeks?	Yes OR Unclear Go to Next question No **Exclude**
5. Did the control group receive the same care (e.g., chemotherapy and supportive therapies) with or without placebo?	Yes OR Unclear Go to Next question No **Exclude**
OUTCOMES IN THE STUDY 6. Did the study document hematologic response? **Or** Did the study document number of patients or red blood cell units transfused? **Or** Did the study document QUALITY of life?	Yes OR Unclear Go to Next question No **Exclude**
Final Decision 1x 'no' ⇒ **exclude** 1x 'unclear' ⇒ **unclear**	**Include Unclear Exclude**

Inclusion/exclusion criteria

Include
Randomized controlled trials (RCTs).

Exclude
Non-randomized studies, in particular quasi-randomized such as where allocation is based on date of birth or day of the month.
RCTs with 10 or fewer subjects in any study arm at randomization.

Population

- **Include**

Age
Participants of every age will be included.
Careful note will be made as to whether included studies have children (persons <18 years) amongst their study populations.

- **Include**

Disease
Participants diagnosed with malignant disease, using clinical and histological/cytological criteria irrespective of type or stage of the disease or previous therapy will be included.

- **Include**

Level of hemoglobin/anemia and nature of anemia
All participants with anemia or at risk of anemia from chemotherapy, and/or radiotherapy or the underlying malignant disease will be included. Other causes of anemia such as hemolysis, iron deficiency and occult bleeding should have been excluded in participants to included studies. Studies where the mean or median hemoglobin is >13 g/dl will be excluded.

Exclude
Studies where erythropoietin is being given in the context of myeloablative chemotherapy ahead of bone marrow or peripheral blood stem cell transplantation will be excluded.

Exclude
Studies where erythropoietin is being given for short-term preoperative treatment to correct anemia or to support collection of autologous blood prior to cancer surgery will also excluded.

Intervention

Epoetin alfa and epoetin beta and darbepoetin alfa based therapies at doses and duration indicated in their license/approval.

Comparator

Any comparator will be acceptable, provided the only difference in initial treatment between treatment and control arms is the use of erythropoietin.
The most common comparator anticipated will be no erythropoietin followed by best standard care where red blood cell (RBC) transfusion will be given when a study participant's hemoglobin falls to an unacceptably *low level* (often 10g/dl). Ideally a protocol for when blood should be instigated should be described. The same rules on rescue RBC transfusion should also apply in the erythropoietin arm.

Concomitant supportive treatments such as G-CSF or iron supplementation will be allowed provided they have been applied equally in each arm of the study. Their presence/absence will be carefully recorded. Studies where concomitant supportive treatments are just applied in one or the other arm alone will be excluded.

Outcomes

Outcomes sought from studies that meet the inclusion criteria are as follows:

- Hematologic response to treatment [Hb increase of 2g/dL or Hct increase of 6%]
- Need for blood transfusion after treatment
- Health-related quality of life
- Fatigue
- Survival
- Tumor response
- Adverse events/toxicity [thrombotic events, hypertension, hemorrhage/thrombocytopenia, rash/irritation/pruritus, seizures]
- Patient preference

Accurate information on patient preference may be scant in the absence of crossover trials. We are not aware of any in this topic area.

All outcomes will be considered in two groups of time periods: outcomes measured up to 6 months and outcomes measured beyond 6 months.

Extractor initials: Date:

Section 1: Paper details

Section 1. Paper details.

Paper title:	
Ref manager number and initials:	
First Author:	
Authors contact address (if available)	
Publication year	
Full text article or only published as an abstract	
Number of trials included in this paper: (if more than one, complete separate extraction forms for each, and add letters A, B, C, etc to the paper name)	
Papers of other trials with which this may link: (if other papers report further results of this trial, incorporate them onto this form, and note what has been here)	
Trial design: Singlecentre or multicentre	
Source of participants (inpatients or outpatients)	
Method of recruitment:	
Dates for recruitment:	
Funding: pharmaceutical or not (give details);	
In industry submission?	
In Cochrane Review? If yes is it an included study, an excluded study or ongoing trial?	

Aim of study:

Details of comparisons evaluated in this trial:

	X = yes	comments
Epoetin versus placebo		
Epoetin versus no treatment		
Epo versus standard care		
Epo versus administration		
Epo versus brand		
Epo versus dose		
	x = yes	comments
Epoetin plus RBC Transfusions in all arms		
Epoetin plus iron suppl. in all arms		
Epoetin plus G-CSF in all arms		
Epoetin plus other		

Eligibility criteria – describe in text box below:

Exclusion criteria - describe in box below:

How was epo deficiency derived? ie tested for epo or diagnosed by elimination of other causes of anaemia?

Staging evaluation:

Histology/Cytology Yes or no
Describe
Was compliance assessed?
If so describe:

Section 2: Outcomes sought

Outcomes	
Primary	
Secondary	
QoL	

Describe statistics used:

Any power calculations and if so for what?

Time periods of surveillance – describe

Maximum duration of surveillance:

Notes:
Dichotomous data: N/n: number of events/total number of patients
Continuous data: N/n/SD: treatment mean of outcome parameter/total number of patients in group/treatment standard deviation of outcome parameter.

Section 3. Intervention

	Intervention	Control		comments
	Group 1[n=] (%)	Group [n=](%)		
Intervention/control				
Epo Dose IU/kg				
Epo dose frequency				
Epo dose per week IU/kg				
Duration of epo treatment (weeks)				
Dosing regimen*				
Route (s.c or iv)				
RBC transfusion trigger ? if so what ?				
iron supplementation? if so describe				

***Dosing regimen:**
Fixed (F): all patients were given continuously the same dose of Epoetin
Decreasing (D): patients with a defined response were given a reduced amount of Epoetin
Increasing (I): patients showing no response within a specified period of time were given an increased dose of Epoetin

Notes: e.g. *describe dosing regime:*

1. Chemotherapy:

Chemotherapy regime describe:

Cycles repeated (days):

Times:

Adjustments:

Notes:

(if stated add the number of pts on each chemo regime)

{describe}		Intervention {}	Control {}	comments
Please give numbers and percentages		Group 1 [n=] (%)	Group [n=] (%)	Group 2 [n=] (%)
Chemo agents (list) ↓	Dose/route/time schedule			

2. Radiotherapy:
Radiotherapy regimen

Radiation repeated every days

Times:

Adjustments:

Notes:

(if stated add the number of pts on each chemo regime)

{describe}		Intervention {}	Control {}	comments
Please give numbers and percentages		Group 1 [n=] (%)	Group [n=] (%)	
Radiotherapy regime (list) ↓	Dose/route/time schedule			

Section 4. Results - Patient Characteristics

Comment: number of patients evaluated usually varies in each outcome

Number of patients recruited for this study:	
Number of patients randomised:	
Number of patients evaluated:	
Number of patients recruited for QoL:	
Number of patients evaluated in QoL	

{}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	comments
Total Patients randomised			
Total Patients evaluated			
Total Patients not evaluated			
Exclusions Reasons:			
Withdrawals reasons:			
Lost to follow up reasons:			

Were the withdrawals and losses to follow up less than 10% of the study population?:

Characteristics at baseline: *Comment: this was designed to fit also studies with several treatment arms add extra columns if need be.*

{describe}	Intervention {}	Control {}	comments
Please give numbers and percentages	Group 1 [n=] (%)	Group [n=] (%)	
Age (state if mean; median; range)			
Gender M / F	/	/	/
Disease category-/ Solid or haem			
List diseases ↓			
Disease Stage			
I			
II			
III			
IV			
Bone Marrow Involvement			
Performance status (Karnofsky, etc			
0			
1			
2			
3			
4			
No. with previous epo therapy (describe if details given)			
No. with previous transfusion			
n = transfusion at baseline (give Hb value for pts with previous transfusion)			
Hb baseline (all patients)			
Hb baseline (no prior transfusion/n patients)			
HKT baseline			
serum EPO, no. pts tested			
serum EPO baseline			
serum iron baseline			
serum ferritin baseline			

Are these characteristics roughly balanced between the groups?:

Section 4. Results – Outcomes

Maximum duration of surveillance:
Describe surveillance: ie time on epo, time after trial stopped

dichotomous data: N/n : number of events/total number of patients in group
continuous data: N/n/SD : treatment mean of outcome parameter/ total number of patients in group/treatment standard deviation of outcome parameter

Haematologic response:

	Definition
complete response	
partial response	
no response	

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
overall response			
complete response			
partial response			
no response			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Haemoglobin:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Hb (g/dl) Baseline			
Hb (g/dl) Finish of epo therapy*(put time point in brackets)*			
Hb (g/dl) Endpoint *(put time point in brackets)*			
Hb change *(g/dl) if stated in the paper (put time point in brackets)* {SD}			
Other time points			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Haematocrit:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Hematocrit Baseline			
Hematocrit Finish of epo therapy*(put time point in brackets)*			
Hematocrit Endpoint *(put time point in brackets)*			
Hematocrit Change if stated in the paper *(put time point in brackets)* {SD}			
Other time points			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Transfusion:

{describe}	Intervention {}	Control {}	comments
	Group 1 [n=] (%)	Group [n=] (%)	
Number of Patients transfused			
Number of RBC-units transfused			
Number of RBC-units transfused per patient			
Number of RBC-units transfused/patient/4weeks			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Quality of Life / Performance status

Quality of life outcomes

{describe}	Intervention {}	Control {}	p-value	comments
	Group 1 [n=] (%)	Group [n=] (%)		
QoL Baseline				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
QOL Score - endpoint				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
QOL Score - overall				
FACT G – 27 items				
Domain 1				
Domain 2				
Domain 3				
Domain 4				
FACT F – 13 items				
Performance				
Score				
Endpoint				
Performance				
Score				
Change				

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Tumour response

Reported?:

	Definition
CR **complete response**	
PR **partial response**	
NR **no response**	
When was tumour response assessed, ie at end of study, at n weeks?	
How was tumour response assessed? clinical exam, radiotherapy, computer tomography, other?	

{describe}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value
CR			
PR			
NR			

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Mortality
Reported?:

{describe} **Cause of death**	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Adverse events:
document during which period the adverse events occurred: during study period, after completion of study

{describe}	Intervention {}	Control {}	Comments, p-value
	Group 1 [n=] (%)	Group [n=] (%)	
Hypertension (definition)			
Rash/Irritation			
Pruritis			
Mortality			
Thrombotic Event (Definition)			
Seizure			
Haemorrhage/Thrombopenia			
Fatigue: Definition:			
EPO Antibodies			

Other adverse events:

{describe}	Intervention {} Group 1 [n=] (%)	Control {} Group [n=] (%)	Comments, p-value

Data extracted from which text, table, figure?

Expert statistical attention needed?

Notes:

Survival
Reported?:

Main results	**HR**	**CI**	**p**	**Comments (inc details)**
Unadjusted (logrank or M-H)				
Stratified				
Cox model				

Other data	**Group 1**	**Group 2**	**Total**	**Comments (inc details)**
Number of events				
Number analysed				
Median survival				
Follow-up (min/max/median)				
Proportions alive at t				
Kaplan Meier curves?				
Other survival curves?				

Summary data estimates				
Method	**O-E**	**V**	**Favours...**	**Comments (inc details)**

*complete one sheet for each comparison between groups

Comments

Section 5 - Study validity form

TREATMENT ALLOCATION	Yes	No	Unclear	Comments
1. Was allocation truly random? Yes: random numbers, coin toss, shuffle etc No: for patient number, date of birth, alternate Unclear: if the method of randomisation was not stated or unclear				
2. Was the treatment allocation concealed? Yes: central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialist allocating treatment could not be aware of the treatment Inadequate: allocation was alternate (by patient, day of the week, admission on ward, etc) or based on information, such as date of birth, already known to the trialist) Unclear: insufficient information given				
SIMILARITY OF GROUPS				
3.Were the patients characteristics at baseline similar in all groups?				
IMPLEMENTATION OF MASKING				
4. Was the treatment allocation masked from the participants? (either stated explicitly, or an identical placebo is used)				
5. Was the treatment allocation masked from the clinicians?				
COMPLETENESS OF THE TRIAL				
6. Were the number of withdrawals, drop outs and lost to follow up in each group stated? NB: Yes, if there have not been any drop outs or lost to follow up				
7. Did the analysis include an intention-to-treat analysis and were there less than 10% of patients per study arm excluded?				

KQ2 and KQ3 Sample Data Abstraction Forms

Paper details

Paper title:	
Ref manager number and initials	
First Author:	
Authors contact address (if available)	
Publication year	
Full text article or only published as an abstract	
Number of trials included in this paper:	
Papers of other trials with which this may link: **(if other papers report further results of this trial,** **incorporate them onto this form, and note what has been here)**	
: Singlecentre or multicentre	
Source of participants (inpatients or outpatients)	
Method of recruitment:	
Dates for recruitment:	
Funding: pharmaceutical or not (give details);	
In industry submission?	

Outcomes sought

Aim of study:

To demonstrate superiority of correction/maintenance vs standard-weekly dose based on proportion of patients requiring:	
Outcomes	•
Secondary	
QoL	

Patient eligibility criteria

•

Patient exclusion criteria - describe in box below:

•

Describe statistics used:

•

Any power calculations and if so for what? / Other comments

Section 3. Intervention

Sample	Intervention	Control	comments
Intervention/control			
Pat randomized			
Initiating Darbepoetin			
Single Dose IU			
dose frequency			
Dose per week			
Duration of epo treatment (weeks)			
Dosing regimen*			
Route (s.c or iv)			
Cumulative Dose Median / trial			
RBC transfusion trigger ? if so what ?			
iron supplementation? if so describe			

***Dosing regimen:**
Fixed (F):all patients were given continuously the same dose of Epoetin
Decreasing (D): patients with a defined response were given a reduced amount of Epoetin
Increasing (I): patients showing no response within a specified period of time were given an increased dose of Epoetin
Notes: e.g. *describe dosing regime:*

Time periods of surveillance – describe

Screening	
Random test period	
Test / treatment:	
Observation period	

Maximum duration of surveillance:

Quality Assessment

Remarks

Characteristics of included studies

Appendix B. Sample Data Abstraction Forms (continued)

study author	participants randomised	drug	Intervention Front Loading	Control Continious dose	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
Sample											

study author	n randomised	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline High	Hb baseline low)	hb category	In arm age reported (mean, SD) range if not reported otherwise	control arm age reported (mean or median, SD), range	age category (children , adults, eldery (>65)
Sample											

study author	Random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality
Sample							

Hematologic Response

Definition as protocol

study author	Hb response definition	Intervention n	Intervention N	Proportion (%)	Control n	Control N	Proportion (%)	Comments

Other definitions

study author	Hb response definition		Hb response n Intervention		Hb response Control		Hb response, comments	
Sample	Mean Hb end of treatment		11,5 (CI 11,4 11,6)		11,7 (11,6 ; 11,8)		In Poster	
Sample								

Subgroups:

Participants receiving red blood cell transfusions

Study ID	Intervention n	Intervention N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Sample							

Subgroups:

Quality of Life (QoL):

Only Graph on copy similar increase FACT AN F Subscale score

	Baseline Intervention	Change Intervention	Baseline Control:	Change: Control	p-value	comments
??						
??						

Tumor response

For Q3 not regularly assed and also not reported.

Overall survival

study author	randomized	Evaluated	method	follow up	events INTERVENTION (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Sample								

Adverse effects

Thromboembolic

Baseline HB: Target Hb: Intervention Hb

Study ID	Intervention n	Intervention N	Percentage (%)	Control n	Control N	Percentage (%)	Definition of	Comments
Sample								

Hypertension

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Hypertension	Comments
Sample								

Rash

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of	Comments
Sample								

Seizures

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of	Comments
Sample								

Cost

Not / reported

KQ4 Sample Data Abstraction Forms

KQ4 Sample Abstraction Forms, Study Characteristics, Part I

Study author	Type of underlying study (basic population)	Type of predictive factors study	Objective as defined by study authors	Drug	Dose per week	Duration of EPO medication	Dose adjustment	Transfusion trigger	Type of publication	Outcomes of the underlying study	Cancer details

KQ4 Sample Abstraction Forms, Study Characteristics, Part II

Underlying therapy	N of patients in underlying study (randomized or included if no randomization)	N of patients analyzed for predictive factors	Hb eligibility criteria	Hb baseline [mean g/dl (SD) if not stated otherwise]	Age [median (range) if not stated otherwise]	HR overall (patients treated with Epo)	Number of patients with Epo dose adjustment	Hb response definition	Comment	Related publications	Checked

KQ4 Sample Abstraction Forms, Study Quality, Part I

study author	Type of predictive factors study	Refutable hypotheses reported	Objective prospectively defined	Inclusion criteria defined for predictive factors study	Sample size calculation (method)	Number and characteristics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	Follow-up at least four weeks	Selection process of possible predictive factors explained and adequate

KQ4 Sample Abstraction Forms, Study Quality, Part II

Cut-off values for continuous variables explained and adequate	Performance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis	Prognostic variables fully defined	Confidence intervals reported	Multivariable analysis				
					Statistical package used	Coding of variables reported	Problem with overfitting	Conformity of linearity for ranked variables reported	Tests of interaction performed

KQ4 Sample Abstraction Forms, Serum Epo, O/P level

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments	Conclusions

KQ4 Sample Abstraction Forms, Ferritin, Iron, Transferrin

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [ferritin] (e.g. likelihood ratio)	Result [iron] (e.g. likelihood ratio)	Result [transferrin] (e.g. likelihood ratio)	Result [transferrin saturation] (e.g. likelihood ratio)	Comments	Conclusions

KQ4 Sample Abstraction Forms, Soluble Transferrin Receptor (sTFR)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum sTFR) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments	Conclusions

KQ4 Sample Abstraction Forms, Blood Count (ex. Hb or RBC)

study author	Cut-off value (value)	Type of cells	N patients responded above cut-off	N patients responded below cut-off	Result (e.g. likelihood ratio)	Comments	Conclusions

KQ4 Sample Abstraction Forms, Creatinine Clearance

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [creatinine clearance] (e.g. likelihood ratio)	Result [serum creatinine] (e.g. likelihood ratio)	Comments	Conclusions

KQ4 Sample Abstraction Forms, Other Baseline Parameters

study author	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Comments	Conclusions

KQ4 Sample Abstraction Forms, Early Changes

study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter

KQ4 Sample Abstraction Forms, Algorithms

study author	Algorithm	Result (e.g. likelihood ratio)	Comment

KQ4 Sample Abstraction Forms, Overview, Part I

			Association?		Cut-Offs											
Study Author	Comment	Patients in predictive factor study	Pos?	Neg?	Pos?	Neg?	O/P	Reference to?	Pos?	Neg?	Ferritin	Pos?	Neg?	Iron	Pos?	Neg?

KQ4 Sample Abstraction Forms, Overview, Part II

Transferrin	Pos?	Neg?	Transferrin Saturation	Pos?	Neg?	sTFR	Pos?	Neg?	Reticulocytes	Pos?	Neg?	Leukocytes	Pos?	Neg?

KQ4 Sample Abstraction Forms, Overview, Part III

Platelets	Pos?	Neg?	Neutrophils	Pos?	Neg?	Creatinine	Pos?	Creatinine clearance	Pos?	Interleukin-1	Pos?	Interleukin-6	Pos?	TNF	Pos?	Others

KQ4 Sample Abstraction Forms, Overview, Part IV

Hb increase after 2-3 weeks	Pos?	Hb increase after 4 weeks	Pos?	Serum ferritin absolute after 2 weeks	Pos?	Reticulocyte increase after 2 weeks	Pos?

KQ4 Sample Abstraction Forms, Sample Sizes, Part I

EPO		O/P		Ferritin		Cell sounts		Creatinine		HB after 2-3 weeks	
Sample size	N studies	Sample size	N studies	Sample size	N studies	Sample size	N studies	Sample size	N studies	Sample size	N studies

KQ4 Sample Abstraction Forms, Sample Sizes, Part II

Hb after 4 weeks		Ret after 4 weeks		Ferritin after 2 weeks		Other early		Algorithm	
Sample size	N studies	Sample size	N studies	Sample size	N studies	Sample size	N studies	Sample size	N studies

Appendix C. Evidence Tables

Table C1. KQ1: Number of studies and randomized patients comparing darbepoetin versus epoetin, epoetin versus control, and darbepoetin versus control, summarized by outcomes reported

Outcome	Darbepoetin (1) vs. Epoetin (2) (R=randomized; E=evaluated)				Epoetin (1) vs. Control (2) (R=randomized; E=evaluated)				Darbepoetin (1) vs. Control (2) (R=randomized; E=evaluated)			
	#RCTs	Total N	N (1)	N (2)	#RCTs	Total N	N (1)	N (2)	#RCTs	Total N	N (1)	N (2)
Effectiveness Outcomes												
hematologic response rates[1]	3	R:645 E:634	R:404 E:397	R:241 E:237	15	R:3,508 E:3,293	R:2,016 E:1,844	R:1,492 E:1,449	3	R:674 E:659	R:439 E:427	R:235 E:232
transfusion rates	6	R:2,375 E:2,158	R:1,322 E:1,169	R:1,053 E:989	34	R:5,280 E:5,210	R:2,902 E:2,859	R:2,378 E:2,351	4	R:994 E:950	R:598 E:566	R:396 E:384
tumor response rates	0				5	R:788 E:688	R:391 E:345	R:397 E:343	1	R:320 E:315	R:159 E:156	R:161 E:159
overall survival	1	R:358 E:358	R:180 E:180	R:178 E:178	35[2]	R:6,964 E:6,918	R:3,850 E:3,825	R:3,114 E:3,093	4	R:994 E:911	R:598 E:583	R:396 E:328
quality of life	2	R:1,342 E:810	R:705 E:433	R:637 E:377	13	R:2,947 E:2,374	R:1,558 E:1,274	R:1,389 E:1,100	2	R:663 E: 558	R: 332 E: 279	R:331 E:279
Adverse Events												
thromboembolic events	3	R:1,896 E:1,879	R:953 E:948	R:943 E:931	30	R:6,168 E:6,092	R:3,395 E:3,355	R:2,773 E:2,737	1	R:320 E:314	R:159 E:155	R:161 E:159
hypertension	0				15	R:1,975 E:1,949	R:1,169 E:1,156	R:806 E:793	1	R:320 E:314	R:159 E:155	R:161 E:159
thrombocytopenia/hemorrhage	0				9	R:1,434 E:1,422	R:835 E:830	R:599 E:592	0			
rash	0				6	R:533 E:522	R:317 E:306	R:216 E:216	0			
seizures	1	R:127 E:127	R:96 E:96	R:31 E:31	3	R:389 E:389	R:198 E:198	R:191 E:191	0			
antibodies[3]	4	R:1,967 E:1,967	R:1,114 E:1,114	R:853 E:853	6	R:1,305 E:1,305	R:704 E:704	R:601 E:601	4	R:994 E:994	R:598 E:598	R:396 E:396

[1] defined as Hb increase $\geq$2 g/dL from baseline (see Methods for details)

[2] Cazzola 1995 randomized 117 patients to 4 epoetin arms, plus 29 patients to control. Two treatment arms were excluded from all analyses but survival, since epoetin dose was <300 IU/Kg per week. However, Cazzola et al. only reported survival data pooled across all treatment arms, precluding exclusion of the low-dose arms. Thus, Cazzola 1995 randomized 146 patients for survival and 86 for all other outcomes.

[3] Reports generally did not specify the number of patients evaluated for antibodies, and included mostly qualitative statements (e.g., "no antibody formation observed"). Absent information, the review assumed all randomized patients were evaluated.

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I

study author	n randomized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Aravantinos 2003	47	24	23	Epoetin alfa (assume)	3 x 150 IU/kg/wk sc	weight	NR, approx. >9-12	decreasing: stopped if Hb >14 g/dl, restarted with 25% reduction when Hb <12.5 g/dl	fix	Hb < 9g/dL or discretion of physician	Hb, Hct, RBCT
Bamias 2003	144	72	72	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	21 to 24 wks (duration of chemo), categorized as >20	decreasing: if Hb increased by 2 g/dl dose reduced to 50% reduction, stopping: if Hb > 15 g/dL epo stopped and resumed at 50% dose when Hb <13g/dl	NR	discretion of physician	Hb, RBCT (QoL in a subset)
Boogaerts 2003, Coiffier 2001	262	133	129	Epoetin beta	3 x 150 IU/kg/wk sc	weight	12	Increasing: if Hb increase <0.5 g/dL within 3-4 wks or <1 g/dL within 6-8 wks dose increased to 300 IU/kg. Decreasing: if Hb increase >2 g/dL within 4 wks dose reduced by 50%. If Hb >14 g/dL stopped and reinstated at 50% if Hb <12 g/dL	as necessary	Hb <8.5 g/dL	Hb, RBCT, QoL
Carabantes 1999	35	20	15	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	during 6 cycles of CT, cycle length 21-28 days, assumed 18 - 24 wk	increasing: if no response dose increased to 3 x 300 IU/kg/wk	not reported	NR	Hb, RBCT, QoL
Cascinu 1994	100	50	50	Epoetin alfa	3 x 100 IU/kg	weight	9	decreasing: if Hb >12g/dl stopped until Hb level deceased <10 g/dl	as necessary	Hb <8g/dL or clinical symptoms	Hb, RBCT, AE
Case 1993	157	81	76	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	decreasing: if Hct 38% was reached dose could be reduced to maintain Hct level	as necessary	at discretion of physician	Hb, RBCT, QoL, AE

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Cazzola 1995 c	146	c: 31, d: 26 (arms a and b excluded)	29	Epoetin beta	7 x 5,000 IU/wk, 7 x 10,000 IU/wk sc	fixed	8	decreasing: if Hb increased >2 g/dL OR Hb level >12.5 g/dL dose was reduced from 7x to 3x per week. If Hb >13 g/dl (MM) or >15 g/dL (NHL) drug was stopped	as necessary	at discretion of physician	Hb, RBCT, AE
Chang 2005	354	176	178	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	16, max 28	Increasing: if at the end of week 4 or 6 Hb had decreased > 2 g/dl dose increased to 60,000 IU Decreasing: If Hb > 14 g/dl stopped until ≤12g/dl, then restart with 75%. If Hb increased > 2 g/dl per month dose reduced by 25%	as necessary	Hb <8g/dL or discretion of physician	QoL, Hb, safety
Dammacco 2001	145	69	76	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	Increasing: if Hb did not increase dose increased to 3 x 300 IU/kg/wk	as necessary	Hb < 7 g/dL or cardiovascular symptoms	Hb, RBCT, QoL, AE
Del Mastro 1997	62	31	31	Epo, unclear whether alfa or beta	3 x 150 IU/kg/wk sc	weight	14	Stopping: if Hb increased >15g/dl in two consecutive weeks drug was stopped until Hb <13 g/dL	as necessary	Hb < 8g/dL or anemia related symptoms	Hb, RBCT, QoL, AE
Dunphy 1999	30	15	15	unclear, assume Epoetin alfa as partly sponsored by OrthoBiotech	3 x 150 IU/kg/wk sc	weight	6	Increasing: if Hb fell ≥ 1g/dl during first course, Epo increased to 3 x 300, if Hb fell >1g/dl during second course, Epo increased to 3 x 450	fix	Hb < 8g/dL or cardiovascular symptoms	Hb, RBCT

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
EPO-CAN-15	106	53	53	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	12-24	Administered if Hb <14 g/dl, increase to 60,000 if Hb < 14 after 3 wks, stopping: if Hb > 16 stop until Hb < 14, then resume at lower dose	not reported	NR	progression free survival, tumour response, overall survival, local disease progression, Hb
EPO-CAN-20	66	assume 33	assume 33	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	12	Initiate if Hb <12 g/dl, if after 4 wks Hb increase < 1 g/dL increase 60,000; if Hb 14 stop until Hb 12 g/dL, resume at 75%	not reported	NR	NR
EPO-GBR-7	301	assume 151	assume 150 assume	Epoetin alfa	if hb < 12.5 then 3 x 10,000 IU (25% of patients) ;if hb > 12.5 then 3 x 4,000 IU (75% of patients) sc	fixed, dependent on Hb	through the end of radiotherapy, not categorized	Titration: to achieve and maintain Hb 12.5 g/dl to 15 g/dl, initiate at Hb level 15g/dL	not reported	NR	local disease free survival, QoL
GOG-0191	113	58	55	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	NR	Titration to maintain >13 g/dl, initiate at Hb level 12 g/dl, stop if Hb > 14 g/dL for 2 weeks or more, reinstate if Hb < 13 g/dL at same dose	not reported	NR	Hb, survival, progression free survival, local tumor control, quality of life

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Henke 2003	351	180	171	Epoetin beta	3 x 300 IU/kg/wk sc	weight	7-9, median duration of epo tx: 42.5 days	Stopping: stop if Hb level >14g/dL (women) or 15g/dL (men), or if Hb increase >2g/dL/wk, resumed if Hb fell below target	as necessary	NR	progression free survival, survival, tumour response, Hb, AE
Henry 1995	132	67	65	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	Decreasing: if Hct 38% was reached drug stopped until Hct < 38%	as necessary	at discretion of physician (result: epo Hct 24.7%, control Hct 25.45)	Hb, RBCT, QoL, AE
Henze 2002	232	assume 116	assume 116	Epoetin alfa	1 x 600 or 900 IU/kg/wk (sc (?))	weight	20	NR	NR	NR	transfusion rates, volume of transfusion, Hb change
Huddart 2002	90	assume 45	assume 45	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	given for 4-6 cycles of chemotherapy plus 4 wks, max 28 wks	Increasing to 3 x 20,000 IU/wk depending on response	NR	NR	Hb response, Hb change, transfusion, QoL (FACT An)
Iconomou 2003	122	61	61	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	12	Increasing: if Hb increase < 1 g/dL dose increased to 3 x 20,000 IU; decreasing: if Hb increased >2g/dL dose reduced by 25%	fix	Hb 7.5 g/dL or discretion of physician	QoL, Hb change, transfusion requirement, outpatients setting

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experim ental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
INT-1	246	80 (150 IU/kg) + 85 (300 IU/kg)	81	Epoetin alfa	a: 3 x 150 (n=85); b: 3 x 300 IU/kg (n=80) sc	weight	1 month post chemotherapy, categorized as unclear	increasing: if reticulocyte after 4 weeks < 40,000 double dose (for 150 arm), stopping: if Hb > 14 g/dL stop until Hb < 12.5 g/dL then restart at 75%	NR	NR	RBCT
INT-3	201	136	65	Epoetin alfa	3 x 150-300 IU/kg sc	weight	12	increasing: if reticulocyte after 4 weeks < 40,000 double dose, stopping: if Hb > 14 g/dL (w) or > 16 g/dL (m) stop until Hb < 12 g/dL (w) or 14 g/dL (m) then restart at 75%	NR	MR	RBCT
Janinis 2003	372	assume 186	assume 186	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	NR	NR	fix	NR	QoL, RBCT, tumor response, "clinical benefit ratio"
Kunikane 2001 a, b	72	assume 48	assume 24	Epoetin beta	a: 3 x 100 IU/kg/wk, b:3 x 200 IU/kg/wk sc	weight	6	stopping: if Hb >16 g/L (men) or >14 g/dL (women) drug was stopped	not reported	NR	Hb, pts RBCT,
Kurz 1997	35	23	12	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	increasing: if Hb increase < 1 g/dL after 4 weeks dose increased to 3 x 300 IU	as necessary (for non-responders), before categorized as fix	Hb < 8 g/dL or clinical symptoms	Hb, RBCT

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Leyland-Jones 2003	939	469	470	Epoetin alfa	1x 40,000 IU/wk sc	fixed	median duration 52 weeks	increasing: if Hb increase <10.5 g/dL after 4 wks drug increased to 60,000 IU/wk, decreasing: if Hb level >14 g/dL or increase > 2 g/dL drug withheld	NR	NR	Survival, QoL, hematological effects, transfusions, time to progression, AE
Littlewood 2001	375	251	124	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	28	stopping: if Hb level increased to >15 g/dL drug was stopped and restarted if Hb 12 g/dL	as necessary	Hb < 8 g/dL or clinical symptoms	Hb, RBCT, QoL, AE, after protocol amendment also survival
Machtay 2004	148	assume 74	assume 74	Epoetin alfa	1x 40,000 IU/wk sc	fixed	9-10, categorized as 6-9	decreasing: if Hb $\geq$ 16 g/dL (men) or >14 g/dL (women) drug stopped, if Hb <13.5 g/dL (men) or <12.5 d/dL (women) dosing resumed at a dose reduction of 30,000 IU	not reported	NR	1 year local progression free survival, survival, Hb , toxicity, patterns of failure
N93-004	224	109	115	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12 (assumed as drug given during 3 x 3 wks chemo plus 3 wks)	decreasing: dose withheld if Hb >16 g/dL and restarted at 50% if Hb <14 g/dL	not reported	NR	Tumour response, overall survival, Hb, transfusion rate
Oberhoff 1998	218	114	104	Epoetin beta	7 x 5,000IU/ wk sc	fixed	12	not reported	as necessary	discretion of physician	Hb, RBCT, AE

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
O'Shaughnessy 2005	100	51	49	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	12	Increasing, decreasing: If Hb increased < 1 g/dl (for baseline Hb 9-12 g/dL) OR < 2 (for baseline Hb 12-14) within 4 wks, drug increased to 60,000 IU; decreasing: If Hb > 15 g/dl drug stopped and reinstated at 85% if Hb < 13g /dl. If Hb increased > 1.3 g/dl in 2 wks dose reduction at physician's discretion.	as necessary	if Hb < 8 g/dL and patient received RBC excluded from study	cognitive function, QoL
Osterborg 1996 a,b	144	95	49	Epoetin beta	a: 7 x 10,000 IU/wk sc, b: titration	fixed, titration	24	increasing: if no signs of response within 4 weeks, dose increased to 300; decreasing: if Hb increase >2 g/dL per 4 weeks dose reduced by 50%. If Hb level >14 g/dL study drug was stopped, if Hb level <13 g/dL reinstated at 50%	not reported	Hb < 10 g/dL	Hb, RBCT, AE
Osterborg 2002, Osterborg 2005	349	173	176	Epoetin beta	3 x 150 IU/kg/wk sc	weight	16	increasing: if no signs of response within 4 weeks, dose increased to 300; decreasing: if Hb increase >2 g/dL per 4 weeks dose reduced by 50%. If Hb level >14 g/dL study drug was stopped, if Hb level <13 g/dL reinstated at 50%	as necessary	Hb < 8.5 g/dL or medically indicated	Hb, RBCT, AE
P-174	45	assume 33	assume 12	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	epoetin alfa dose titrated to maintain Hct between 38%-40%	not reported		Hb
Quirt 1996	56	assume 28	assume 28	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	16	increasing: if Hb increase <1 g/dL within 4 wks drug increased to 300 IU/kg	not reported	NR	Hb, RBCT, QoL

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Razzouk 2004	224	113	111	Epoetin alfa	1 x 600 IU/kg/wk U IV	weight	16	increasing: if Hb increase <1 g/dL within 4 wks drug increased to 900 IU/kg, maximal 60,000 IU iv qw; decreasing: if Hb > 15 g/dL drug withheld, restarted if Hb < 13 g/dL with 25% dose reduction	as necessary	NR	Hb, QoL
Rose 1994	221	142	79	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	12	epoetin alfa dose titrated to maintain Hct between 38%-40%	as necessary	NR	HR, RBCT, QoL
Rosenzweig 2004	27	14	13	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	12	Increasing: if Hb increased <1 g/dL after 4 weeks, drug increased to 1 x 60,000 IU/wk, if Hb increase < 1 g/dL after 8 weeks, drug discontinued	NR	at discretion of physician	fatigue, QoL
Savonije 2004	315	211	104	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	14	Increasing: if Hb increase <1 g/dL after 4 wks drug increased to 20,000 IU tiw; decreasing: if Hb > 14 g/dL drug withheld until Hb < 13 g/dL, resumed at 10,000 IU twice weekly	not reported	NR	Hb, transfusion requirements, QoL
Silvestris 1995	54	30	24	Epoetin alfa	3 x 150 IU/kg/wk sc	weight	24	Increasing: dose was increased after the 6th week of treatment	fix	NR	Hb, AE
Ten Bokkel 1998 a, b	122	88	34	Epoetin beta	a: 3 x 150 IU/kg/wk, b: 3 x 300 IU/kg/wk sc	weight	through duration of chemotherapy plus 3-24, categorized as more than 20 weeks	Decreasing: if Hb increased $\geq$2 g/dL dose was reduced by 50%. If Hb level >15g/dl drug stopped until Hb <14g/dl	as necessary	usually if Hb < 9.7 g/dl	RBCT, transfusion, AE

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Thatcher 1999 a, b	130	86	44	Epoetin alfa	a: 3 x 150 IU/kg/wk, b: 3 x 300 IU/kg/wk sc	weight	26	Decreasing: if Hb exceeded 15 g/dl drug stopped and restarted with 50% if Hb <13 g/dL	as necessary	Hb $\leq$ 10 g/dL	Hb, RBCT, QoL, AE
Thomas 2002	130	65	65	Epoetin alfa	3 x 10,000 IU/wk sc	fixed	not clearly reported, outcomes assessed at 12 weeks	NR	not reported	at discretion of physician	Hb, QoL, RBCT
Throuvalas 2000	55	assume 28	assume 27	unclear, Epoetin alfa or beta	5 x 10,000 IU sc	fixed	during chemotherapy, 5-6 weeks	NR	as necessary	Hb < 9.0 g/dl	Hb, RBCT
Vadhan-Raj 2004	60	29	31	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	16 wks or up to 4 wks post surgery, categorized as 16 weeks	Increasing: if Hb level $\leq$13 g/dL after 4 wks increase to 60,000 IU/wk; decreasing: if Hb level $\geq$15 g/dL withheld and resumed if Hb $\leq$14 g/dl at 50% dose.	not reported	NR	Hb response, transfusions, local tumour response, pathological post-surgery response, QoL, safety
Welch 1995	30	15	15	Epoetin alfa	3 x 300 IU/kg/wk sc	weight	24	Decreasing: if Hb > 15 g/dl drug stopped until Hb between 12 -14 g/dl, drug reinstated at 50% dose reduction	as necessary	discretion of physician	Hb, RBCT, AE

Appendix C. Evidence Tables

Table C2. KQ1: Epoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n random-ized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Witzig 2005	344	174	170	Epoetin alfa	1 x 40,000 IU/wk sc	fixed	16	Increasing: if Hb increase < 1 g/dL after 4 weeks dose increased to 60,000 IU; if Hb level >15g/dL for two weeks, drug stopped and restarted with 75% when Hb <13 g/dl	fix	at discretion of physician	QoL, transfusions, Hb change
Wurnig 1996	30	16	14	Epoetin alfa	2 x 600 IU/kg/wk IV	weight	20	Maintaining: epo was started if Hb <11 g/dl and discontinued if Hb >13.5 g/dl	no	Hb level 8.5 g/dL	Hb, RBCT, AE

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Aravantinos 2003	47	ovarian, lung, stomach, other	solid	Platinum based chemotherapy	Hb <10.5 g/dL	9.8 (+/- 0.5)	9.32 (+/- 0.8)	10	59 (18-76)	64 (23-75)	adults
Bamias 2003	144	ovarian, NSCLC, SCLC, other	solid	Platinum based chemotherapy	Hb <13 g/dL	11.5 (range 11.1, 11.9)	11.5 (range 11.2, 11.8)	10-12	60 (18-77)	62 (19-80)	adults
Boogaerts 2003, Coiffier 2001	262	MM, NHL, CLL, Ovarian, bone, GI, respir, other	mixed	Chemotherapy, platinum & non platinum, details not reported but interpreted as such as some solid cancers which are usually treated with platinum are included	Hb ≤11 g/dl	9.0 (range 5-13)	9.2 (range 5-12)	10	62 (24-68)	62 (24-85)	adults
Carabantes 1999	35	SCLC, ovarian	solid	Platinum based chemotherapy	Hb ≤11.5 g/dl	10.5 (+/- 0.8)	10.5 (+/- 0.8)	10-12	NR	NR	adults
Cascinu 1994	100	stomach, ovarian, melanoma, head neck, lung, breast	solid	Platinum based chemotherapy, some, additional radiotherapy, categorized as chemo-platinum all	Hb ≤9 g/dl	8.63 (+/- 0.62)	8.73 (+/- 0.52)	10	median 58 (44-72)	median 57 (45-68)	adults
Case 1993	157	solid and hemato-logical tumors	mixed	Chemotherapy without platinum	Hb ≤10.5 g/dl	9.29 (SD 1.14)	9.57 (SD 1.04)	10	64 (27-92)	64 (30-88)	adults
Cazzola 1995 c	146	MM, NHL	hemato-logical	Chemotherapy without platinum, some (22%) patients did not receive chemotherapy, categorized as platinum free chemotherapy	Hb ≤11 g/dl INDEPENDENT OF TRANSFUSION	c: 9.4 (SD 1.9); d: 9.4 (SD 1.0)	9.5 (SD 1.1)	10	c: median 31 (42-85); d: median 63 (28-80)	median 68 (28-82)	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Chang 2005	354	Breast cancer, stage I-IV	solid	Chemotherapy without platinum	Hb <12g/dL	11.2 (SD 0.9)	11.3 (SD 0.8)	10-12	50.4 (SD 11.1, R 27-78)	50.1 (SD 10, R 31-85)	adults
Dammacco 2001	145	MM, NHL	hemato-logical	Chemotherapy, platinum & non platinum	Hb ≤10 g/dl	8.67 (SD 0.9)	8.34 (SD 1.4)	10	60.6 (SD 8.3), range 39-74	65 (SD 8.8), range 47-85	adults
Del Mastro 1997	62	breast, stage II	solid	Chemotherapy without platinum	Hb ≥12g/dL	13.00 (0.7)	13.1 (0.6)	12	median 54 (31-66)	median 56 (29-68)	adults
Dunphy 1999	30	head neck, SCLC, stage III/IV	solid	Platinum based chemotherapy	NR	14.1 (2.1)	14.1 (1.6)	12	median 59 (42-76)	median 67 (32-82)	adults
EPO-CAN-15	106	limited disease SCLC	solid	Platinum based chemotherapy plus radiotherapy, categorized as chemo_radio	NR	NR	NR	NR (no assumption possible)	NR	NR	adults
EPO-CAN-20	66	advanced SCLC	solid	Radiotherapy +/- non platinum based chemotherapy, categorized as chemo-radiotherapy only	Hb ≤12 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
EPO-GBR-7	301	head and neck, stage I'-IV	solid	Radiotherapy	Hb ≤15 g/dl	13.4 (SD 1.2)	13.5 (SD 1.3)	12	59.8 (SD 10.8)	60.2 (SD 10.6)	adults
GOG-0191	113	cervix carcinoma	solid	Platinum based chemotherapy plus radiotherapy, categorized as chemo_radio	Hb ≤14 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
Henke 2003	351	advanced (stage III , IV) head and neck	solid	Radiotherapy after surgical resection, 22% (78/351) of patients radiotherapy only	<13 g/dL (men), <12 g/dL (women)	median 11.7 (8.5 –14.4)	median 11.8 (6.9 – 14.6)	10-12	median 58 (25-81)	median 57 (36-87)	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Henry 1995	132	solid and hematological tumors	mixed	Platinum based chemotherapy	Hb ≤10.5 g/dl	9.68 (SD 1.28)	9.27 (SD 1.49)	10	60 (20-84)	60 (34-83)*	adults
Henze 2002	232	ALL (37%) and non-ALL malignancies	mixed	Chemotherapy, some non-ALL patients underwent also surgery, categorized as unclear	NR	NR	NR	NR (no assumption possible)	NR	NR	children
Huddart 2002	90	solid tumours, no details given	solid	Platinum based chemotherapy	Hb <10.5 g/dL	NR	NR	NR (no assumption possible)	NR	NR	adults
Iconomou 2003	122	lung, breast, colorectal, ovarian, unknown primary, kidney, stomach, other	solid	Chemotherapy, platinum & non platinum (51/122 (42%) received platinum)	Hb ≤11.0g/dL	10.1 (+/- SD 0.6)	10.1 (+/- SD 0.4)	10-12	60.6 (SD 10.7), range 33 - 85	62.6 (SD 10.3), range 34-80	adults
INT-1	246	ovarian	solid	Platinum-based chemotherapy	Hb ≤ 11 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
INT-3	201	mixed	mixed	Chemotherapy unclear	Hb ≤ 12 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
Janinis 2003	372	solid and hematological malignancies	mixed	Chemotherapy, platinum & non platinum (129/372 (35%) received platinum)	Hb ≤11.0 g/dL	median 10.5	median 10.5	10-12	NR	NR	adults
Kunikane 2001 a, b	72	SCLC	solid	Platinum based chemotherapy	Hb 9-13 g/dl	a: 12.3 (SD 1.2), b: 12.3 (SD 1.4)	12.0 (SD 0.9)	12	a: 62.7 (SD 8.7), b: 62.7 (SD 4.8)	59.5 (SD 9.9)	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Kurz 1997	35	solid tumours; ovarian, uterus, cervix	solid	Platinum based chemotherapy, 6/35 (17%) did not receive platinum, categorized as platinum	Hb ≤11 g/dl	9.88 (SD 0.8)	9.85 (SD 0.6)	10	54.4 (SD 9.7)	52.7 (SD 7.5)	adults
Leyland-Jones 2003	939	metastatic breast cancer	solid	Chemotherapy without platinum	Hb 13 g/dL, no upper of lower limit on Hb for inclusion	median 12.8	median 12.8	12	55.8 (SD 11.13)	55.1 (SD 10.49)	adults
Littlewood 2001	375	NHL, MM, breast, HD, CLL, GI, other	mixed	Chemotherapy without platinum	Hb ≤10.5 g/dl OR 10.5-12 AND decrease of ≥1.5 g/dL per cycle	9.9 (SD 1.13)	9.7 (SD 1.13)	10	58.3 (SD 14.8), range 18.7-84.9	59.5 (SD 13.9), range 21.1-88.6	adults
Machtay 2004	148	head and neck non-metastatic, not resected	solid	Radiotherapy, advanced stages received in addition platinum based chemotherapy, categorized as radiotherapy	Hb 9-13.5 g/dL (men), 9-12.5 g/dL (women)	12.0	12.2	12	NR	NR	adults
N93-004	224	SCLC, limited and extended disease	solid	Platinum based chemotherapy	Hb ≤14 g/dl	NR	NR	NR (no assumption possible)	NR	NR	adults
Oberhoff 1998	218	solid tumours; ovarian, breast, lung, GU, GI, other	solid	Chemotherapy, platinum & non platinum	Hb ≤11 g/dl OR ≤13 g/dl AND decrease of ≥1.5 g/dL per CT cycle	median 9.6	median 10.3	10	52, range 20-85	57, range 19-73	adults
O'Shaughnessy 2005	100	breast cancer, stages I-IIIB	solid	Chemotherapy without platinum	Hb 9-14 g/dl	12.8 (SD 1.0)	13.0 (SD 1.0)	12	53.3 (SD 9.7)	54.3 (SD 12.0)	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb base-line EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Osterborg 1996 a,b	144	MM, NHL, CLL	hematological	Chemotherapy without platinum, 6/59 (10%) did not receive chemotherapy, study categorized as chemotherapy non platinum category	Hb ≤10 g/dl	a: median 8.0 (range 6.2-10.1), b: median 8.0 (range 5.5-10.3)	median 8.1 (range 5.2-9.8)	10	a: 66(43-84), b: 65 (38-82)	64 (36-83)	adults
Osterborg 2002, Osterborg 2005	349	MM, NHL, CLL	hematological	Chemotherapy without platinum	Hb ≤10 g/dl	9.2 (SD 1.1)	9.3 (SD 1.0)	10	63 (32-86)	64 (28-83)	adults
P-174	45	CLL	hematological	Chemotherapy (NR, but for some patients reported in Pangalis 1995), categorized as 'unclear'	Hct < 32%	NR	NR	NR (no assumption possible)	NR		adults
Quirt 1996	56	lymphoma, solid tumours	mixed	Chemotherapy, unclear if platinum included or not , categorized as 'unclear' OK	Hb drop of 1.5 g/dL	10.9	10.7	10-12	NR	NR	adults
Razzouk 2004	224	solid tumours, Hodgkin's disease, non-Hodgkin's disease, ALL	mixed	Chemotherapy 'unclear'	Hb ≤12 g/dl	9.8 (SD 1.3)	9.5 (SD 1.0)	10	12.4 (SD 3.6)	10.8 (SD 4.0)	children
Rose 1994	221	CLL, stage III, IV	hematological	Chemotherapy (only 162/221 (73%) received CT), categorized as chemotherapy without platinum	Hct ≤32%	9.1 (1.3)	9.3 (1.2)	10	68.3 (SD 10)	68.1 (9.3)	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Rosenzweig 2004	27	metastatic breast cancer	solid	Chemotherapy, 14/27 (52%) did not receive chemotherapy, categorized as 'unclear'	Hb <12g/dL	NR	NR	NR (no assumption possible)	55.9 (+/-11.7)	53.9 (+/- 14.2)	adults
Savonije 2004	315	solid tumors	solid	Platinum based chemotherapy	Hb <12.1 g/dL	10.7 (SD 1.0)	10.8 (SD 1.0)	10-12	56.9 (SD 10.9)	57.7 (SD 9.5)	adults
Silvestris 1995	54	MM	hemato-logical	Chemotherapy	Hb 8 ≤g/dl	NR	NR	NR (no assumption possible)	NR	adults	adults
Ten Bokkel 1998 a, b	122	ovarian (stage II-IV)	solid	Platinum based chemotherapy	Hb ≤13 g/dl	a: 12.0 (1.3-12.6, SD 0.88), b:11.6 (10.5-12.2, SD 1.34)	11.8 (10.6-12.5, SD 1.19)	10-12	a: 58.81, b: 60.97	58.83	adults
Thatcher 1999 a, b	130	SCLC	solid	Platinum based chemotherapy (89% of patients)	Hb ≥ 10.5 g/dl	a: 13.4 (SD 1.3), b: 13.5 (SD 1.3)	13.4 (SD 1.3)	12	a: 59 (43-72), b: 58.5 (30-72)	60 (39-74)	adults
Thomas 2002	130	NR	unclear	Chemotherapy, categorized as 'unclear'	(Hb inclusion criteria level: < 12g/dL)	10.59 (SD 1.05)	10.59 (SD 1.05)	10-12	NR	NR	adults
Throuvalas 2000	55	cervix and bladder carcinoma	solid	Platinum based chemotherapy plus radiotherapy, categorized as chemo_radio therapy	Hb 10-13 g/dl	11.5 (SD 0.6)	11.1 (0.5)	10-12	54 (36-75)	58 (35-75)	adults
Vadhan-Raj 2004	60	gastric or rectal ca	solid	combined chemo-radio therapy without platinum, categorized as chemo_radio	Hb 10-15 g/dl	median 13	median 13	12	NR	NR	adults

Appendix C. Evidence Tables

Table C3. KQ1: Epoetin versus Control, Study Characteristics, Part II (cont'd)

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	Hb category	AGE; EPO arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Welch 1995	30	ovarian, stage II-IV	solid	Platinum based chemotherapy	normal Hb	13	12.8	12	NR	NR	adults
Witzig 2005	344	lung, breast, other	solid	Chemotherapy, platinum & non platinum, some radiotherapy, 56/330 (175) received platinum	Hb ≤11.5 g/dl (men), Hb ≤10.5 g/dl (women)	9.5 , range 6.0-11.4	9.4 , range 6.9-11.4	10	63.6 (SD 11.89), range 20-88	63.7 (SD 13.00), range 24-86	adults
Wurnig 1996	30	various malignant one tumours	solid	Chemotherapy, platinum & non platinum, 21/35 (60%) received platinum	Hb 11 g/dl	11.0 (SD 1.5)	10.5 (SD 0.75)	10-12	NR	NR	adults

Appendix C. Evidence Tables

Table C4. KQ1: Darbepoetin versus Control, Study Characteristics, Part I

study author	n randomized	n randomized in experimental arm	n randomized in control arm	drug	dose	weight based or fix	duration of study drug medication (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Hedenus 2002 a,b,c	66	all 55, a: 11, b:22, c:22	11	Darbepoetin alfa	a: 1.0, b: 2.25, c: 4.0 µg/kg qw sc	weight	12	Decreasing: if Hb increase >2 g/dL in 4 wks drug reduced by 50%, if Hb level >15 g/dL (men) or 14 g/dL (women) drug stopped and reinstated at 50% if Hb <13 g/dL	as necessary	Hb <8g/dL	dose response relationship Hb response, Hb change, transfusion
Hedenus 2003	349	176	173	Darbepoetin alfa	2.25 µg/kg/ qw sc	weight	12	Increasing: if Hb increase <1.0 g/dL within 4 wks of treatment dose was doubled. Decreasing: if Hb increase >15 g/dL (men) or >14g/dL (women) drug stopped until Hb <13 g/dL and reinstated at 50%	as necessary	Hb <8g/dL or discretion of physician	Hb response, transfusion, Hb change, QoL
Kotasek 2003 a,b,c,d,e,f	259	208	51	Darbepoetin alfa	a: 4.5 µg/kg Q3W, b:6.75 µg/kg Q3W, c: 9 µg/kg Q3W, d:12 µg/kg Q3W, e:13.5 µg/kg Q3W, f:15 µg/kg Q3W sc	weight	12	Increasing not allowed, decreasing: if Hb increased >15 g/dL (men) or >14 g/dl (women) drug stopped and reinstated at a lower dose level if Hb <13 g/dL	NR	NR	Safety, antibodies, Hb response, Hb change, transfusions, QoL

Appendix C. Evidence Tables

Table C4. KQ1: Darbepoetin versus Control, Study Characteristics, Part I (cont'd)

study author	n randomized	n random-ized in experi-mental arm	n random-ized in control arm	drug	dose	weight based or fix	duration of study drug medi-cation (weeks)	dose adjustment	iron	transfusion trigger	primary and secondary outcomes of the study
Vanstee nkiste 2002	320	159	161	Darb-epoetin alfa	2.25 mcg/kg qw sc	weight	12	Increasing: if Hb increase < 1 g/dL within 6 wks dose doubled to 4.5 µg/kg/wk. Decreasing: If Hb >15 g/dl (men) or >14 g/dl (women) drug stopped, reinstated at 50% if Hb <13 g/dl	NR	Hb < 8g/dL or at discretion of physician	transfusion, number of RBCTs, Hb response, AE, overall survival, progression free survival, QoL, hospitalization

Appendix C. Evidence Tables

Table C5. KQ1: Darbepoetin versus Control, Study Characteristics, Part II

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline EPO arm [mean g/dl (SD)]	Control arm mean baseline HB (SD)	hb category	AGE; darbepo arm, as reported (mean, SD) range if not reported otherwise	AGE; control arm, as reported (mean or median, SD), range	age category (children, adults, elderly (>65)
Hedenus 2002 a,b,c	66	lymphoma, HD, NHL, CLL, MM	hematological	Chemotherapy without platinum	Hb ≤11.0 g/dL	a: 9.7 (SD 0.8), b: 9.4 (SD 1.3), c: 9.7 (SD 0.9)	9.5 (SD 2.0)	10	a: median 64 (26 to 80), b: median 69 (20 to 84), c: median 70 (52-84)	median 63 (25-80)	adults
Hedenus 2003	349	lymphoma: HD, NHL, MM	hematological	NR, assumed to be chemotherapy without platinum	Hb ≤11.0 g/dL	9.59 (SD 1.22)	9.5 (SD 1.21)	10	64.8 (SD 13.8)	64.6 (SD 12.2)	adults
Kotasek 2003 a,b,c,d,e,f	259	breast, gyne, gastrointestinal, lung, other	solid	Chemotherapy, not reported if with or without platinum, interpreted as some patients receiving platinum as some of solid cancers included are usually treated with platinum	Hb ≤11.0 g/dL	9.93 (SD 1.0)	9.87 (SD 1.12)	10	58.3 (SD 11.9)	56.2 (SD 12.4)	adults
Vansteenkiste 2002	320	SCLC, and non-SCLC	solid	Platinum based chemotherapy	Hb ≤11.0 g/dL	10.28 (SD 1.08)	9.93 (SD 1.01)	10-12	61.6 (SD 9.2)	61.3 (SD 8.8)	adults

Appendix C. Evidence Tables

Table C6. KQ1: Darbepoetin versus Epoetin, Study Characteristics, Part I

study author	# random-ized	design	drug	Darbepoetin dose per week	Epoetin dose per week	weight based or fix	duration of medication (weeks)	Dose adjustment Darbepoetin	Dose adjustment Epoetin	iron	transfu-sion trigger	primary and secondary outcomes of the study
Alexopoulos 2004	50	compare effectiveness, RCT	Darbepoetin versus epoetin alfa	1 x 150 µg qw	10,000 IU tiw	darb fixed, epo fixed	12	Increasing: if Hb increase < 1.5 g/dL at 4 wks drug increased to 300 µg qw	Increasing: if Hb increase < 1.5 g/dL at 4 wks drug increased to 20,000 IU tiw	NR	NR	Hb, RBCT, QoL
Glaspy 2002, Part A	269	sequential dose finding study	Darbepoetin versus epoetin alfa	a: 0.5; b: 1.0; c: 1.5; d: 2.25; e: 4.5; f: 6.0 and g: 8.0 µg/kg qw	150 IU/kg tiw	darb weight based, epo weight based	12	no dose adjustment	Increasing: if Hb increase < 1.0 g/dL at wk 8 EPO increased to 300 IU/kg tiw	NR	NR	safety, Hb, RBCT, QoL
Glaspy 2002, Part B	160	parallel dose finding study	Darbepoetin versus epoetin alfa	a: 3.0; b: 5.0; c: 7.0 and d: 9.0 µg/kg q2w	40,000 IU qw	darb weight based, epo fixed	12	no dose adjustment	Increasing: if Hb increase < 1.0 g/dL at wk 6 EPO increased to 60,000 IU qw	NR	NR	safety, Hb, RBCT, QoL
Glaspy 2003 a-c	127	pilot front loading study	Darbepoetin versus epoetin alfa	a: 4 x 4.5 µg/kg qw until Hb ≤ 12 g/d/L, then 1.5 µg/kg qw up to wk 12; b: 4 x 4.5 µg/kg qw, then 8 x 2.25 µg/dL; c: 4 x 4.5 µg/kg qw, then 8 x 3 µg/dL qw	40,000 IU qw	darb weight based, epo fixed	12	drug was withheld if Hb level > 15.0 g/dL (men) or 14 g/dL (women), if Hb ≤ 13 g/dL drug reinstated at 75%; no other dose adjustment	Increasing: if Hb increase < 1.0 g/dL at wk 6 EPO increased to 60,000 IU qw; decreasing: drug was withheld if Hb level > 15.0 g/dL (men) or 14 g/dL (women), if Hb ≤ 13 g/dL drug reinstated at 75%	NR	Hb ≤ 8 g/dL or as medically indicated	Hb, time to response, safety, QoL

Appendix C. Evidence Tables

Table C6. KQ1: Darbepoetin versus Epoetin, Study Characteristics, Part I (cont'd)

study author	# random-ized	design	drug	Darbepoetin dose per week	Epoetin dose per week	weight based or fix	duration of medication (weeks)	Dose adjustment Darbepoetin	Dose adjustment Epoetin	iron	transfu-sion trigger	primary and secondary outcomes of the study
Glaspy 2005*	1220	phase 3, non-inferiority trial	Darbepoetin versus epoetin alfa	1 x 200 µg q2w	40,000 IU qw	darb fixed, epo fixed	12 or 16	remain at randomized dose OR dose may be increased to 300 µg q2w	remain at randomized dose OR dose may be increased to 60,000 IU qw	NR	NR	RBCT, safety, Hb response, change, QoL
Schwartzberg 2004, a-c	318	to validate patient questionnaire	Darbepoetin versus epoetin alfa	200 mg q2w	40,000 IU qw	darb fixed, epo fixed	16	Increasing: if Hb increase $\leq$ 1.0 g/dL at wk 4 Darb increased to 300µg q2w; Stopping: drug was withheld if Hb level > 13.0 g/dL and reinstated at the previous dose if Hb $\leq$ 13 g/dL.	Increasing: if Hb increase $\leq$ 1.0 g/dL at wk 4 EPO increased to 60,000 IU qw; Stopping: drug was withheld if Hb level > 13.0 g/dL and reinstated at the previous dose if Hb $\leq$ 13 g/dL.	NR	NR	validate patient satisfaction questionnaire, efficacy (Hb, Hct, RBCT), safety

*study was amended from 12 to 16 weeks to allow dose titrations to occur by physician discretion, to increase sample size, to modify secondary Hb efficacy endpoint

Appendix C. Evidence Tables

Table C6. KQ1: Darbepoetin versus Epoetin, Study Characteristics, Part I (cont'd)

study author	# random-ized	design	drug	Darbepoetin dose per week	Epoetin dose per week	weight based or fix	duration of medication (weeks)	Dose adjustment Darbepoetin	Dose adjustment Epoetin	iron	transfu-sion trigger	primary and secondary outcomes of the study
Waltzman 2005	358	effectiveness study to compare Hb response rates	Darbepoetin versus epoetin alfa	200 mg q2w	40,000 IU qw	darb fixed, epo fixed	12 to 16	Increasing: if Hb increase < 1.0 g/dL at wk 6 Darb increased to 300µg q2w; Decreasing: if Hb rise > 1.0 g/dL in 2 wks dose decreased by 25%; Stopping: drug was withheld if Hb level > 13.0 g/dL resumed at 25% dose reduction when Hb < 12 g/dL.	Increasing: if Hb increase < 1.0 g/dL at wk **4** EPO increased to 60,000 IU qw; Decreasing: if Hb rise > 1.0 g/dL in 2 wks dose decreased by 25%; Stopping: drug was withheld if Hb level > 13.0 g/dL, resumed at 25% dose reduction when Hb < 12 g/dL.	NR	NR	Hb response, RBCTs, change, QoL

Appendix C. Evidence Tables

Table C7. KQ1: Darbepoetin versus Epoetin, Study Characteristics, Part II

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline Darb arm [mean g/dl (SD)]	Hb baseline EPO arm [mean g/dl (SD)]	Hb category	Age Darb arm [mean (SD)] if not stated otherwise	Age EPO arm [mean (SD)] if not stated otherwise	age category (children , adults, elderly (>65)
Alexopoulos 2004	50	non-hematological tumors	solid	NR	Hb ≤11 g/dL OR Hb decrease ≥ 1.5 g/dL during CT	10.2 (+/-0.87)	9.81 (+/-1.02)	10	NR	NR	adults
Glaspy 2002, Part A	269	Breast, GI, lung, other	solid	chemotherapy	Hb ≤11 g/dL	9.91 (SD 0.94)	10.02 (SD 0.88)	10-12	61.9 (SD 11.9)	57.8 (SD 14.5)	adults
Glaspy 2002, Part B	160	breast, GI, lung, other	solid	chemotherapy	Hb ≤11 g/dL	9.82 (SD 0.95)	9.73 (SD 1.17)	10	64.3 (SD 12.0)	63.9 (SD 12.3)	adults
Glaspy 2003 a-c	127	breast, lung, GI, gyne, GU, other cancers	solid	chemotherapy	Hb ≤11 g/dL	a: 9.54 (SD 1.12); b: 9.90 (SD 1.02); c: 9.90 (SD 0.99)	9.84 (SD 0.83)	10	a: 60.5 (SD 14.1); b: 66.4 (SD 12.7); c: 62.7 (SD 13.2)	63.5 (SD 8.7)	adults
Glaspy 2005	1220	lung, breast, GI, gyne, lymphoproliferative (7.5%), other cancers	solid or mixed	some (42%) platinum based chemotherapy	Hb ≤11 g/dL	10.18 (SD 0.90)	10.21 (SD 0.89)	10-12	63.2 (SD 12.4)	63.7 (SD 11.6)	adults

Appendix C. Evidence Tables

Table C7. KQ1: Darbepoetin versus Epoetin, Study Characteristics, Part II (cont'd)

study author	n random-ized	cancer details	cancer category	therapy	Hb eligibility criteria	Hb baseline Darb arm [mean g/dl (SD)]	Hb baseline EPO arm [mean g/dl (SD)]	Hb category	Age Darb arm [mean (SD)] if not stated otherwise	Age EPO arm [mean (SD)] if not stated otherwise	age category (children , adults, elderly (>65)
Schwartzberg 2004, a-c	318	a: breast cancer, b: lung cancer (stage IIIb, IV), c: gynecological cancers	solid	chemotherapy, some platinum (41%)	Hb ≤ 11 g/dL	10.4 (SD 0.8)	10.4 (SD 0.8)	10-12	58.7 (SD 11.5)	61.7 (SD 12.1)	adults
Waltzman 2005	358	lung, breast, other	solid	chemotherapy, some platinum (40.5%)	Hb ≤ 11 g/dL	10.02 (SD 0.84)	10.14 (SD 0.75)	10-12	63.4 (SD 11.8)	62.1 (SD 11.8)	adults

Appendix C. Evidence Tables

Table C8. KQ1: Epoetin versus Control, Study Quality

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
Aravantinos 2003	unclear	unclear	no	no placebo	yes	yes	low	full text publication
Bamias 2003	unclear	unclear	no	no placebo	yes, exception TR, QoL	control group had statistically significant lower EPO levels at baseline (EPO: 24,8 (16.6-37), control: 12.5 (8.7-18), mU/ml, geometric mean, p=0.012)	low	full text publication
Boogaerts 2003, Coiffier 2001	yes	yes	no	no placebo	yes	more patients in control (80%) had CT before study compared to EPO (68%), p=0.025	low	full text publication, abstract publication, unpublished data, FDA documents
Carabantes 1999	unclear	unclear	no	no placebo	yes, exception QoL	yes	low	abstract
Cascinu 1994	yes	yes, sealed envelopes	double	Placebo	yes	yes	high	full text publication, unpublished data
Case 1993	yes	yes	double	Placebo	yes	yes, no details for cancer stage available	high	full text publication, unpublished data, FDA documents
Cazzola 1995 c	yes	unclear	no	no placebo	yes	yes	low	full text publication, unpublished data, FDA documents
Chang 2005	unclear	unclear	no	no placebo	yes	patients with metastatic disease appear to have lower baseline Hb at entry and significantly higher level of serum ferritin, more cycles of chemotherapy were given in the epo arm (mean 5.0 vs 4.6, p=0.058)	low	full text publication
Dammacco 2001	yes	unclear	double	Placebo	yes, exception: Hb response	yes	high, low for Hb response	full text publication, unpublished data, FDA documents
Del Mastro 1997	yes	yes	no	no placebo	yes	yes	low	full text publication, unpublished data
Dunphy 1999	unclear	unclear	no	no placebo	yes	gender was not distributed equally, more male patients in EPO arm (80% vs 47%, p0.003)	low	full text publication
EPO-CAN-15	unclear	unclear	double	Placebo	yes	unclear	high	FDA documents
EPO-CAN-20	unclear	unclear	double	Placebo	yes	unclear	high	FDA documents

Appendix C. Evidence Tables

Table C8. KQ1: Epoetin versus Control Study Quality (cont'd)

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
EPO-GBR-7	unclear	unclear	no	no placebo	yes, not TVE and TR	more subjects in the EPO arm had tumour stage IV (39% vs 36%)	low	FDA documents
GOG-0191	unclear	unclear	no	no placebo	yes	unclear	low	FDA documents
Henke 2003	unclear	unclear	double	Placebo	yes	more smokers (66% vs 53%) in the EPO group; more stage IV patients in the EPO hypopharynx subgroup (85% vs 70%)	high	full text publication, FDA documents
Henry 1995	yes	yes	double	Placebo	yes	yes, no details for cancer stage available	high	full text publication, unpublished data, FDA documents
Henze 2002	unclear	unclear	no	no placebo	unclear	unclear, non-ALL patients underwent surgery, this might have biased the transfusion outcome	low	abstract
Huddart 2002	unclear	unclear	no	no placebo	unclear	unclear	low	abstract
Iconomou 2003	yes (was performed by a telephone call to the registry of the department of medicine)	yes (was performed by a telephone call to the registry of the department of medicine)	no	no placebo	yes	yes ("Univariate analyses revealed no significant differences at baseline between groups for any of the demographic and clinical characteristics […].")	low	full text publication
INT-1	unclear	unclear	double	Placebo	yes	unclear	high	FDA documents
INT-3	unclear	unclear	double	Placebo	yes	unclear	high	FDA documents
Janinis 2003	unclear	unclear	no	no placebo	unclear	yes ("Both groups were well balanced for performance status, gender, age, and tumor type.")	low	abstract
Kunikane 2001 a, b	yes, centrally randomized	yes, centrally randomized	double	Placebo	no	yes	low	full text publication

Appendix C. Evidence Tables

Table C8. KQ1: Epoetin versus Control Study Quality (cont'd)

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
Kurz 1997	yes	yes	double	Placebo	yes	yes	high	full text publication, unpublished data
Leyland-Jones 2003	unclear	unclear	double	Placebo	yes	EPO patients were more likely to have adverse factors such as advanced age, lower performance status, greater extent of disease at baseline, and more risk factors for TVE's (based on retrospective chart review)	high	full text publication, FDA documents
Littlewood 2001	yes	yes	double	Placebo	yes	yes	high	full text publication, unpublished data, FDA documents
Machtay 2004	unclear	unclear	no	no placebo	yes	unclear	low	abstract, FDA documents
N93-004	unclear	unclear	double	Placebo	yes	slightly higher proportion of patients in the EPO arm had extensive SCLC than in the placebo arm (66% vs 59%)	high	FDA documents
Oberhoff 1998	yes	yes	no	no placebo	yes	yes	low	full text publication, unpublished data, FDA documents
O'Shaughnessy 2005	yes, computer generated randomization schedule	unclear	double	Placebo	yes	yes	high	full text publication
Osterborg 1996 a,b	yes	yes	no	no placebo	yes	yes	low	full text publication, unpublished data, FDA documents
Osterborg 2002, Osterborg 2005	yes	yes	double	Placebo	yes	yes	high	full text publication, unpublished data, FDA documents
P-174	unclear	unclear	double	Placebo	yes	unclear	high	FDA documents
Quirt 1996	unclear	unclear	double	Placebo	yes	unclear	high	abstract
Razzouk 2004	unclear	unclear	double	Placebo	yes	unclear	high	abstract

Appendix C. Evidence Tables

Table C8. KQ1: Epoetin versus Control Study Quality (cont'd)

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
Rose 1994	yes	unclear	double	Placebo	yes	yes	high	abstract, unpublished data, FDA documents
Rosenzweig 2004	unclear	yes (using sequential, opaque, sealed envelopes with the order unknown to the investigator)	no	no placebo	yes	yes	low	full text publication, FDA documents
Savonije 2004	unclear	unclear	no	no placebo	yes	significantly more patients with metastatic disease in EPO group	low	abstract
Silvestris 1995	unclear	unclear	no	no placebo	no, not sure	unclear	low	full text publication
Ten Bokkel 1998 a, b	yes	yes	no	no placebo	yes, exception TR	yes	low	full text publication, unpublished data, FDA documents
Thatcher 1999 a, b	yes	yes	no	no placebo	yes	yes	low	full text publication, unpublished data, FDA documents
Thomas 2002	unclear	unclear	no	no placebo	yes	yes ("At baseline, groups balanced for Hb, demographics, CT and disease related variables.")	low	abstract
Throuvalas 2000	yes	yes	no	no placebo	yes	yes	low	abstract, unpublished data
Vadhan-Raj 2004	unclear	unclear	double	Placebo	yes	unclear	high	abstract, FDA documents
Welch 1995	unclear	unclear	no	no placebo	yes	yes	low	full text publication
Witzig 2005	unclear	unclear	double	Placebo	yes (not QoL)	yes	high, low for QoL	full text publication, FDA documents
Wurnig 1996	yes (computer-generated randomization code)	unclear	double	Placebo	yes	unclear	high	full text publication

Appendix C. Evidence Tables

Table C9. KQ1: Darbepoetin versus Control, Study Quality

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
Hedenus 2002 a,b,c	yes (central randomization service)	yes (central randomization service)	double	Placebo	yes	yes	high	full text publication
Hedenus 2003	yes (central randomization service)	yes (central randomization service)	double	Placebo	yes	more patients with indolent lymphoma were randomized to placebo and more patients with higher stage of disease were randomized to Aranesp	high	full text publication, FDA documents
Kotasek 2003 a,b,c,d,e,f	unclear	unclear	double	Placebo	yes for safety, not for transfusion	slightly higher proportion of patients in the 12 µg group had breast cancer (61%) compared with the other groups, which ranged from 15 to 38%. The 12 µg group had also a slightly higher mean hb at baseline (10.4 g/d, compared with the other groups (9.7 to 10.2).	high, low for transfusion	full text publication
Vansteenkiste 2002	yes, central randomization service	yes, central randomization service	double	Placebo	yes (not QoL)	yes	high, low for QoL	full text publication, FDA documents

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Table C10. KQ1: Darbepoetin versus Epoetin, Study Quality

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality	publication
Alexopoulos 2004	unclear	unclear	no	no placebo	ITT	yes	low	abstract
Glaspy 2002	unclear	unclear	no	no placebo	ITT or 10%	yes	low	full text
Glaspy 2003 a-c	unclear	unclear	no	no placebo	ITT or 10%	exception: lower mean baseline Hb and lower baseline serum erythropoietin concentration in darb group a and a larger proportion of women in the darb cohorts	low	full text
Glaspy 2005	unclear	unclear	no	no placebo	ITT or 10%, not for QoL	yes	low	abstract
Schwartzberg 2004	unclear	unclear	no	no placebo	ITT or 10%	yes	low	full text
Waltzman 2005	unclear	unclear	no	no placebo	ITT or 10%, more pts excluded for QoL	exception: higher percentage of patients received nonplatinum based CT in the EPO group	low	abstract

Appendix C. Evidence Tables

Table C11. KQ1 Outcome I. Hematologic response: Epoetin versus Control

study author	Hb response definition	Epo n	Epo N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Hb at baseline < 10 g/dL								
Boogaerts 2003	Hb increase of 2 g/dL during the treatment phase without transfusion requirements after the initial 4 treatment weeks	63	133	47.37%	17	129	13.18%	
Case 1993	Hct increase of 6% from baseline independent of transfusion	46	79	58.23%	10	74	13.51%	
Cazzola 1995 c	Hb increase of 2 g/dL independent of transfusion	19	31	61.29%	2	29	6.90%	data submitted for Cochrane Review
Cazzola 1995 d		16	26	61.54%				data submitted for Cochrane Review
Dammacco 2001	Hb increase of 2 g/dL independent of transfusion	38	66	57.58%	6	66	9.09%	data were included in Cochrane Review as Coiffier 2001
Henry 1995	Hct increase of 6% from baseline independent of transfusion	31	64	48.44%	4	61	6.56%	Hct definition
Littlewood 2001	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	172	244	70.49%	22	115	19.13%	efficacy population: patients on study at least 28 days
Oberhoff 1998	Hb increase of 2 g/dL independent of transfusion	38	114	33.33%	7	104	6.73%	at week 12, data submitted for Cochrane Review
Osterborg 1996 a	Hb increase of 2 g/dL independent of transfusion	21	47	44.68%	8	49	16.33%	data submitted for Cochrane Review
Osterborg 1996 b		23	48	47.92%				
Osterborg 2002	Hb increase of 2 g/dL independent of transfusion within 6 weeks	114	170	67.06%	46	173	26.59%	at end of week 16
Witzig 2004	Hb increase of 2 g/dL from baseline	120	165	72.73%	52	164	31.71%	unclear if independent of transfusion
Rose 1994	Hb increase of $\geq$ 6% of Hct unrelated to transfusion	67	142	47.18%	13	79	16.46%	Hct definitions, data submitted for Cochrane Review

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Table C11. KQ1 Outcome I. Hematologic response: Epoetin versus Control (cont'd)

study author	Hb response definition	Epo n	Epo N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Hb at baseline 10 to 12 g/dL								
Bamias 2003	Hb increase of 2 g/dl	15	72	20.83%	2	72	2.78%	unclear if independent of transfusion
Chang 2004	Hb increase of 2 g/dl independent of transfusion in the previous 28 days	115	175	65.71%	11	175	6.29%	Hb response was evaluated retrospectively
Iconomou 2003	Hb increase of 2 g/dl	25	57	43.86%	7	55	12.73%	after 12 wks of treatment, unclear if independent of transfusion
Savonije 2004	Hb increase of 2 g/dl independent of transfusion in the previous 28 days	146	211	69.19%	32	104	30.77%	

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Table C12. KQ1 Outcome I. Hematologic response: Darbepoetin versus Control

Study Author	Treatment n	Treatment N	Treatment Proportion	Control n	Control N	Control Proportion	Hb definition	Comment
Hedenus 2002a	5	11	45.45%	1	11	9.09%	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	absolute numbers were derived using Kaplan-Meier method; (Arm a 45% N=11, control 10%, N=11)
Hedenus 2002b	12	22	54.55%					arm b: 55%, N=22
Hedenus 2002c	14	22	63.64%					arm c: 62%, N=22
Hedenus 2003	104	174	59.77%	31	170	18.24%	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	Derived using Kaplan-Meier method (darb arm response 60%, N=174, control response 18%. N=170)
Kotasek 2003a	8	32	25.00%	7	51	13.73%		Derived using Kaplan-Meier method; arm a: 24%, N=32, control 14%, N=51
Kotasek 2003b	8	17	47.06%				increase Hb 2 g/dL from baseline during 12 week study in the absence of RBCT in the previous 28 days	c: 50%, N=17
Kotasek 2003c	23	46	50.00%					b: 48%, N=46
Kotasek 2003d	17	28	60.71%					d: 62%, N=28
Kotasek 2003e	20	35	57.14%					e: 58%, N=35
Kotasek 2003f	20	40	50.00%					f: 50%, N=40

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Table C13. KQ1 Outcome I. Hematologic response: Darbepoetin versus Epoetin

study author	Hb response definition	Hb response assessed at week	Darb (n)	Darb (N)	Percentage (%)	EPO (n)	EPO (N)	Percentage (%)	Comments
Hb at baseline ≤ 10 g/dL									
Glaspy 2003 a	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	12	19	32	59.38%	15	30	50.00%	reported K-M percentages with 95% CI, a: 59% (38; 80), EPO 49% (29; 69)
Glaspy 2003 b		12	17	30	56.67%				reported K-M percentages with 95% CI, b: 58% (38; 79)
Glaspy 2003 c		12	20	30	66.67%				reported K-M percentages with 95% CI, c: 65% (47; 84)
Glaspy 2002 Part B a	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	12	20	33	60.61%	19	32	59.38%	a: 3 µg/kg q2w Darb, K-M percentages 60% (39; 80), EPO: 60% (40; 79)
Glaspy 2002 Part B b		12	25	31	80.65%				b: 5 µg/kg q2w Darb, K-M percentages 79% (56; 100)
Glaspy 2002 Part B c		12	18	32	56.25%				c: 7 µg/kg q2w Darb, K-M percentages taken from figure: 55%
Glaspy 2002 Part B d		12	21	32	65.63%				d: 9 µg/kg q2w Darb, K-M percentages taken from figure: 67%

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Table C13. KQ1 Outcome I. Hematologic response: Darbepoetin versus Epoetin (cont'd)

study author	Hb response definition	Hb response assessed at week	Darb (n)	Darb (N)	Percentage (%)	EPO (n)	EPO (N)	Percentage (%)	Comments
Hb at baseline 10-12 g/dL									
Waltzman 2005	Hb increase of $\geq$ 2 g/dL at week 9	9	48	177	27.12%	78	175	44.57%	based on patients who received at least 1 dose of study drug and had at least 1 postbaseline hb or transfusion, p<0.001(logistic regression model adjusted for CT)
Waltzman 2005	Hb increase of $\geq$ 2 g/dL at week 17	17	74	177	41.81%	101	175	57.71%	based on patients who received at least 1 dose of study drug and had at least 1 postbaseline hb or transfusion, p=0.004 (logistic regression model adjusted for CT)

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Table C14. KQ1 Outcome I. Hematologic response studies omitted from meta-analysis: Epoetin versus Control

study author	Hb response definition	Hb response, comments	Hb response n EPO	Hb response n control
Carabantes 1999	Hb increase ≥ 1 g/dl OR Hb increase 0.5-1 g/dl and reticulocyte count increase > 40,000/ml after 3-4 weeks	no data reported	NR	NR
Cascinu 1994	Hb level >10 g/dl after 9 weeks without transfusions		41/50 (82%)	0/50
Del Mastro 1997	maintain Hb level > 10g/dl		31/31 (100%)	15/31 (48%)
Henke 2003	Hb target level reached (women: Hb ≥14g/dL, men Hb ≥15g/dL)		148/180 (82%)	26/171 (15%)
Huddart 2002	Hb increase of 2 g/dl and/or increase in reticulocyte count >40 x 10^9	only % given for response, Epo36%, Control 5.5%, assumed 45 per group (n=90 for total group given in abstract)	16/45 (36%)	2/45 (5.5%)
Kurz 1997	Hb increase of 2 g/dL and/or Hb >12 g/dL	data were included in Cochrane Review but should be excluded	13/23 (56.5%)	0/12
Silvestris 1995	Hb increase of 2 g/dl or not further transfusion		21/27 (77.8%)	NR

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Table C15. KQ1 Outcome I. Hematologic response study omitted from meta-analysis: Darbepoetin versus Control

Study ID	Treatment n	Treatment N	Treatment Proportion	Control n	Control N	Control Proportion	Hb definition	Comments
Vansteenkiste 2002	103	156	66.03%	38	158	24.05%	Hematological response as defined by Hb increase 2 g/dL OR target Hb 12g/dL	not in MA, absolute numbers were derived using Kaplan-Meier method, darb 66%, N=156, control 24%, N=158

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Table C16. KQ1 Outcome I. Hematologic response studies omitted from meta-analysis: Darbepoetin versus Epoetin

study author	Hb response definition	response assessed at week	Darb (n)	Darb (N)	Proportion (%)	EPO (n)	EPO (N)	Proportion (%)	Comments
Schwartzberg 2004	Hb increase of ≥ 2 g/dL OR Hb level ≥12 g/dL		108	157	68.79%	112	155	72.26%	definition did not meet our criteria, percentages reported
Alexopoulos 2004	Hb increase of 1.5 g/dL over baseline	4	8	25	32.00%	3	25	28.00%	reported percentages, p=NS
Alexopoulos 2004		8	11	25	44.00%	11	25	44.00%	reported percentages, p=NS
Glaspy 2005	achieving Hb target ≥ 11 g/dL	K-M approach	547	606	90.26%	576	603	95.52%	K-M proportion (95% CI) Darb: 90.3% (87.5; 93.1), EPO: 95.5 (93.6; 97.4)
Additional data									
Glaspy 2002 Part A	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	12	3	13	23.00%	NR	53	NR	dosage: 0.5 µg/kg qw Darb; K-M 23% (0; 46)
Glaspy 2002 Part A		12	22	29	76.00%				dosage: 4.5 µg/kg qw Darb; K-M 76% (59; 94)

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Table C17. KQ1 Outcome I. Hematologic response subgroup analysis: Epoetin versus Control

Study	Subgroups prospectively stratified for	Epo n/N (%)	Control n/N (%)	p-value
Littlewood 2001	Overall efficacy population	172/244 (70.5%)	22/115 (19.1%)	<0.001
	solid tumors	87/131 (66.4%)	13/61 (21%)	NR
	hematological tumors	85/113 (75.22%)	9/543 (16.6%)	NR
	Hb≤ 10.5	139/293 (47.4%)	22/100 (22%)	NR
	Hb > 10.5	33/41 (80.5%)	0/15 (0%)	NR
Osterborg 2002	All	114/170 (67%)	46/173 (27%)	<0.001
	MM	44/58 (76%)	17/58 (29%)	<0.001
	NHL	33/53 (62%)	12/49 (24%)	<0.001

Osterborg 1996		Dose titration Epo	Dose titration Epo	Fixed dose Epo	Fixed dose Epo	Controls	Controls
		Responder/Treated	Response rate (K-M est)	Responder/Treated	Response rate (K-M est)	Responder/Treated	Response rate (K-M est)
	MM	13/22	70%*	12/23	64%	4/20	21%
	NHL	10/22	52%	7/15	54%	4/19	28%
	Chemotherapy yes	22/38	63%*	18/34	63%*	7/35	24%
	Chemotherapy no	1/6	20%	1/4	33%	1/4	25%

*p<0.05 compared with controls

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Table C18. KQ1 Outcome I. Hematologic response subgroup analysis: Darbepoetin versus Control

Study	Subgroups prospectively stratified for	Epo n/N (%)	Control n/N (%)	p-value
Hedenus 2003	lymphoma	64% (55/86)	13% (11/84)	<0.001
	myeloma	56% (49/88)	22% (20/86)	<0.001

Table C19. KQ1 Outcome I. Hematologic response subgroup analysis: Darbepoetin versus Epoetin

Study	Subgroups prospectively stratified for	Darb n/N (%)	Epo n/N (%)	p-value
Schwartzberg 2004	Overall population	108/157 (69%)	122/155 (72%)	NR
	Lung cancer	63/72 (88%)	56/69 (81%)	NR
	Breast cancer	25/51 (49%)	30/51 (59%)	NR
	Gynecological cancers	21/34 (62%)	26/35 (74%)	NR
	Hb < 10.5	21/38 (55%)	18/38 (47%)	NR
	Hb $\geq$ 10.5	88/119 (74%)	94/117 (80%)	NR

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Table C20. KQ1 Outcome II. Transfusion: Epoetin versus Control

Study ID	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Baseline Hb below < 10g/dL							
Aravantinos 2003	9	24	37.50	23	23	100.00	
Boogaerts 2003	43	133	32.33	67	129	51.94	
Cascinu 1994	*10*	*50*	*20.00*	*28*	*50*	*56.00*	*data submitted for original Cochrane Review*
Case 1993	*32*	*79*	*40.51*	*36*	*74*	*48.65*	*data submitted for original Cochrane Review*
Cazzola 1995c	6	31	19.35	8	29	27.59	
Cazzola 1995d	4	26	15.38				
Dammacco 2001	19	69	27.54	36	76	47.37	
Henry 1995	34	64	53.13	42	61	68.85	
Huddart 2002	18	45	40.00	32	45	71.11	
Kurz 1997	5	23	21.74	8	12	66.67	
Littlewood 2001	62	251	24.70	49	124	39.52	
Oberhoff 1998	*32*	*114*	*28.07*	*44*	*104*	*42.31*	*data submitted for original Cochrane Review*
Osterborg 1996a	*33*	*47*	*70.21*	*39*	*49*	*79.59*	*data submitted for original Cochrane Review*
Osterborg 1996b	*39*	*48*	*81.25*				
Osterborg 2002	*65*	*169*	*38.46*	*90*	*173*	*52.02*	*data submitted for original Cochrane Review*
Witzig 2004	42	166	25.30	65	164	39.63	
Rose 1994	*65*	*142*	*45.77*	*47*	*79*	*59.49*	*data submitted for original Cochrane Review*

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Table C20. KQ1 Outcome II. Transfusion: Epoetin versus Control (cont'd)

Study ID	Treatment n	Treatment N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Baseline Hb below 10-12g/dL							
Bamias 2003	11	72	15.28	24	72	33.33	
Chang 2004	15	175	8.57	40	175	22.86	
Iconomou 2003	9	61	14.75	16	61	26.23	
Ten Bokkel 1998a	2	45	4.44	13	33	39.39	
Ten Bokkel 1998b	6	42	14.29				
Thomas 2000	7	62	11.29	31	65	47.69	
Wurnig 1996	8	15	53.33	14	14	100.00	
Carabantes 1999	4	20	20.00	13	15	86.67	
Janinis 2003	17	186	9.14	43	186	23.12	
Quirt 1996	4	27	14.81	8	27	29.63	
Razzouk 2004	72	111	64.86	85	111	76.58	
Savonije 2004	76	211	36.02	68	104	65.38	
Throuvalas 2000	2	28	7.14	10	26	38.46	
Vadhan-Raj 2004	4	28	14.29	10	31	32.26	
Baseline Hb 12g/dL							
Del Mastro 1997	0	31	0.00	2	31	6.45	
Dunphy 1999	2	13	15.38	5	14	35.71	
Kunikane 2001a	1	16	6.25	0	19	0.00	
Kunikane 2001b	2	18	11.11				
Thatcher 1999a	19	42	45.24	26	44	59.09	
Thatcher 1999b	9	44	20.45				
Welch 1995	4	15	26.67	8	15	53.33	
Baseline not reported							
Henze 2002	72	116	62.07	80	116	68.97	

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Table C21. KQ1 Outcome II. Transfusion: Darbepoetin versus Control

Study ID	Dosage	Treatment n	Treatment N	Treatment Percentage	Control n	Control N	Control Percentage	first 4 weeks included in analysis?	Comments
Hedenus 2002a	1.0 µg/kg qw	3	11	27.27%	5	11	45.45%	excluding first 4 weeks, counting week 5 to end of treatment	derived from K-M estimates, arm a: 27% (95% CI 1-54), N=11, control: 45% (16-75), N=11
Hedenus 2002b	2.25 µg/kg qw	6	22	27.27%					27% (9-46), N=22
Hedenus 2002c	4.5 µg/kg qw	3	22	13.64%					15% (0-30), N=22
Hedenus 2003	2.25 µg/kg/qw	52	167	31.14%	79	165		excluding first 4 weeks, counting week 5 to end of treatment (week 13)	derived from K-M estimates, arm a: 31%(95% CI 24-38), N=167; 48% (95% CI 41%-56%), N=165
Kotasek 2003a	4.5 µg/kg Q3W	8	30	26.67%	23	50		excluding first 4 weeks, counting week 5 to week 12	arm a: 25% (9%-41%), N=30; control 46% (32%-61%), N=50
Kotasek 2003b	6.75 µg/kg Q3W	5	17	29.41%					arm b: 28% (7%-51%), N=17
Kotasek 2003c	9.0 µg/kg Q3W	12	41	29.27%					arm c: 30% (16%-44%), N=41
Kotasek 2003d	12.0 µg/kg Q3W	7	27	25.93%					arm d: 26% (7.5%-41%), N=27
Kotasek 2003e	13.5 µg/kg Q3W	9	35	25.71%					arm e: 27% (11%-40%), N=35
Kotasek 2003f	15 µg/kg Q3W	7	38	18.42%					arm f: 19% (6%-32%), N=38
Vansteen._FDA report	2.25 µg/kg qw	53	156	33.97%	89	158		including first 4 weeks	

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Table C22. KQ1 Outcome II. Transfusion: Darbepoetin versus Epoetin

Study ID	Darbepoetin (n)	Darbepoetin (N)	Percentage (%)	Epoetin (n)	Epoetin (N)	Percentage (%)	Weeks included	Comments
Baseline Hb below < 10g/dL								
Glaspy 2002 Part A, c (1.5 µg/kg/qw)	9	35	25.71%	12	53	22.64%	5-13	K-M percentages reported, a: 26% (9; 43), EPO 23% (10; 36)
Glaspy 2002 Part A, d (2.25 µg/kg/qw)	8	59	13.56%					b: 13% (4; 23)
Glaspy 2002 Part A, e (4.5 µg/kg/qw)	2	29	6.90%					c: 6% (2; 30)
Glaspy 2002 Part B, a (3 µg/kg/q2w)	1	30	3.33%	11	30	36.67%	5-13	K-M percentages reported, a: 4% (0; 11), EPO 36% (10; 87)
Glaspy 2002 Part B, b (5 µg/kg/q2w)	7	30	23.33%					b: 22% (6; 37)
Glaspy 2002 Part B, c (7 µg/kg/q2w)	7	30	23.33%					c: 23% (7; 39)
Glaspy 2002 Part B, d (9 µg/kg/q2w)	3	29	10.34%					d: 11% (0; 23)
Alexopoulos 2004	4	25	16.00%	3	25	12.00%	"during study period"	absolute numbers reported, p=NS
Baseline Hb below 10-12 g/dL								
Schwartzberg 2004 a (breast cancer)	4	72	5.56%	11	69	15.94%	1-16	percentages reported (a: 6% vs 16%, b: 27% vs 18%, c: 21% vs 17%)
Schwartzberg 2004 b (lung cancer)	14	51	27.45%	9	51	17.65%		
Schwartzberg 2004 c (gynecological)	7	34	20.59%	9	51	17.65%		
Glaspy 2005	157	582	26.98%	126	571	22.07%	5 to end of treatment period (wk 17)	K-M percentages reported, darb: 27%, EPO 22%, adjusted for strata Hb </> 10 g/dl and +/- platinum
Waltzman 2005	29	163	17.79%	20	155	12.90%	5 to end of treatment period (wk 17)	p=0.2936 logistic regression, adjusted for CT

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Table C23. KQ1 Outcome II. Transfusion studies omitted from meta-analysis: Epoetin versus Control

Study ID	Epo n/N (%)	Control n/N (%)	Comments
O'Shaugnessy 2005	-/47	4/47 (8.5%)	not in MA, patients receiving transfusion were excluded from study

Table C24. KQ1 Outcome II. Transfusion studies omitted from meta-analysis: Darbepoetin versus Control

Study ID	Treatment n	Treatment N	Treatment Percentage	Control n	Control N	Control Percentage	first 4 weeks included in analysis?	Comment
Vansteenkiste 2002	40	148	27.03%	77	149	51.68%	excluding first 4 weeks, counting week 5 to end of treatment	Based on K-M estimates. Darb: 27% (20% to 35%), N=148, control: 52% (44% to 66%), N=149, Difference of 25% (95% CI 14% to 36%) was statistically significant, p<0.001.

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Table C25. KQ1 Outcome II. Transfusion subgroup analysis: Epoetin versus Control

Study	Subgroups prospectively stratified for	Epo n/N (%)	Control n/N (%)	p-value	comments
Henze 2002	Overall efficacy population	72/116 (62%)	22/115 (19.1%)	p=0.32	overall n=232, not reported how many patients per group
	ALL (37%)	66%	89%	p=0.03	
	non-ALL	56%	60%	p=0.65	
Razzouk 2004	All patients	72/111 (35%)	85/111 (23%)	p=0.0536	p value refers to proportion NOT transfused
	ALL (n=75)	26/40 (65.0%)	22/35 (62.9%)		
Witzig 2004	All patients	42/166 (25.3%)	65/164 (39.6%)	p=0.005	
	mild anemia (Hb > 9 g/dL)	19%	29%		
	severe anemia (Hb < 9 g/dL)	40%	62%		

Table C26. KQ1 Outcome II. Transfusion subgroup analysis: Darbepoetin versus Control

Study Hedenus 2003	Subgroups prospectively stratified for	Epo % (n/N)	Control % (n/N)	p-value
excluding first 4 weeks	lymphoma	27%	49%	0.002
	myeloma	35%	48%	0.042
including first 4 weeks	lymphoma	NR	NR	0.011
	myeloma	NR	NR	0.018

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Table C27. KQ1 Outcome II. Transfusion subgroup analysis: Darbepoetin versus Epoetin

Study	Subgroups prospectively stratified for	Darbepoetin (n)	Darbepoetin (N)	Proportion (%)	Epoetin (n)	Epoetin (N)	Proportion (%)	Comments
Schwartzberg 2004	Overall	25	157	15.92%	26	155	16.77%	weeks 1 to 16, percentages reported
	Hb < 10 g/dL	8	38	21.05%	16	38	42.11%	
	Hb ≥ 10 g/dL	17	119	14.29%	11	117	9.40%	

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Littlewood 2001								
Littlewood 2001, Martin et al 2003	375	375	Kaplan-Meier, unadjusted, p=0.13	26 months median fu, 12 months after last subject completed study	155/251 (62%)	82/124 (66%)	HR 0.81 (0.62; 1.06)	lost to follow up: Epo 2, placebo 1
Littlewood 2001	375	375	Cox-regression, adjusted, p=0.052	26 months median fu, 12 months after last subject completed study	155/251	82/124	HR 1.309 in favor of EPO, equivalent to HR 0.76 (0.58; 1.00)	calculated by GS
Littlewood 2001			median survival		17 months	11 months		
Information submitted by OrthoBiotech for Cochrane Review	NR	NR	Cox model, adjusted, p=0.0296	Nov 15 1998, 3 months after last subject completed study	NR	NR	HR 1.38	
Information submitted by OrthoBiotech for Cochrane Review	375	375	log rank test p=0.128 (unadjusted)	Aug 15 1999; 12 months after last subject completed study	155/251	82/124	NR	
Information submitted by J&J for FDA/ODAC hearing	375	375	proportions alive at	12 months	60%	40%	HR 1.309, p=0.052, in favor of EPO	
Information submitted by J&J for FDA/ODAC hearing	375	375	Hazard ratio	double-blind study phase plus 30 days	41/251	22/124	HR 0.81 (0.48; 1.36)	
Information submitted by J&J for FDA/ODAC hearing	375	375	median survival		17 months	11 months		

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Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Machtay 2004								
Abstract publication 2004	135	135	1-yr actuarial overall survival	1-year	70% (assume survival)	81% (assume survival)	HR 1.57 (0.76; 3.27)	
Abstract publication 2004, additional slides	148	141	deaths within 90 days post study	< 1 year	9/71	6/70	p=0.59	
Abstract publication 2004, additional slides	148	141	2- yr overall survival	median f/u 14.5 months, for surviving patients 19.4 months	27/71 deaths	21/70 deaths	HR 1.41 (0.8; 2.5), p=0.23	
FDA report 2004	135	117	NR	8.7 months	At the interim analysis (at 8.7 months) 22 out of 117 patients had died. The analysis showed no statistically significant differences, but non-significant trends towards lower survival in the epoetin alfa arm.			
Information submitted by J&J for FDA/ODAC hearing	135	135	Proportion	NR	17/67 (25%)	12/68 (18%)	NR	
Leyland – Jones 2003								
Leyland – Jones 2003	939	939	Proportion	4 months	41	16	NR	
Leyland – Jones 2003	939	939	Proportion, p=0.0117	12 months	70% (survival)	76% (survival)	NR	
FDA report and information submitted by J&J for FDA/ODAC hearing	939	939	Proportion	4 months	41/469	16/470	NR	
FDA report and information submitted by J&J for FDA/ODAC hearing	939	939	Cox adjusted for metastatic category (ITT)	12 months	148/469	115/470	HR 1.37 (1.07; 1,74)	

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Witzig 2004								
Witzig 2004	344	333	proportion	died during study period	13/168	8/165	NR	
Witzig 2004	344	333	proportion	died within 30 days after the last dose	31/168	22/165	NR	
Information submitted by J&J for FDA/ODAC hearing	344	333	Hazard ratio	double-blind study phase plus 30 days	31/168	26/165	HR 1.17 (0.69; 1.97)	
Witzig 2004	344	330	proportion	follow up 1 year	105/166	103/164	p=0.53	HR 1.09 (0.83; 1.43) calculated with p value and events, direction questionable
Witzig 2004	344	330	median overall survival	follow up 1 year	10.4 months	11.2 months	p=0.53	
N93-004								
FDA report and information submitted by J&J for FDA/ODAC hearing	224	224	proportion	3 years	100/109	101/115	NR	
FDA report and information submitted by J&J for FDA/ODAC hearing	224	224	median survival (K-M estimate, 95% CI in months)	3 years	10.5 (9; 13)	10.4 (8; 13)	NR	

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Henke 2003								
Henke 2003	351	351	Cox model, adjusted for stratum and AJCC stage, ITT	EPO: 605 days, control 928 days	109/180	89/171	HR 1.39 (1.05-1.84)	
Henke 2003	351	351	Cox model, adjusted for stratum and AJCC stage, radiotherapy correct	EPO: 605 days, control 928 days	109/180	89/171	HR 1.22 (0.86-1.73)	
Henke 2003	351	351	Cox model, adjusted for stratum and AJCC stage, per protocol	EPO: 605 days, control 928 days	109/180	89/171	HR 1.13 (0.78-1.64)	
Information submitted by Roche for FDA/ODAC hearing	351	351	adjusted Cox regression, p=0.023, adjusted by stratum and TNM staging	EPO: 605 days, control 928 days	109/180	89/171	HR 1.39 (1.05-1.84)	censored: EPO 71, control 82
Information submitted by Roche for FDA/ODAC hearing	351	351	log rank test, p=0.0901, not adjusted	EPO: 605 days, control 928 days	109/180	89/171	HR 1.27 (0.96-1.68), calculated	censored: EPO 71, control 82

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Österborg 2002								
Österborg 2002	349	343	proportion	deaths during 16 weeks of study	21/170	19/173	-	
Österborg 2002	349	343	proportion	deaths during 16 weeks of study and follow up	28/170	22/173	-	
IPD data submitted by Roche 2002	349	343	Hazard ratio	median observation time 113 days	21/170	19/173	HR 1.13 (0.61; 2.09)	
Information submitted by Roche for FDA/ODAC hearing	349	343	Cox regression	deaths until day 28 after end of treatment	NR	NR	HR 1.29 (0.71; 2.35)	
Information submitted by Roche for FDA/ODAC hearing	349	343	logrank test p=0.76	median survival (months): EPO 17.4, control 18.3	110/170	109/173	HR 1.04 (0.80; 1.36), calculated by JB	censored: EPO 60, control 64
Österborg 2005	349	343		min follow up 17.5 months, median time for patients being censored EPO 27.8 months. Control 27.5 months; median survival (months): EPO 17.4 (95% CI 15.0; 20.5), control 18.3 (95% CI 16.0-22.3), log-rank test: p=0.76	110/170	109/173	HR 1.04 (0.80; 1.36), reported	censored: EPO 60, control 64

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Cazzola 1995								
Cazzola 1995	146	146	Proportion	NR	4/117	3/29	NR	
IPD data submitted by Roche 2002	146	146	IPD based hazard ratio	median observation time 57 days	2/117	1/29	HR 0.06 (0.00; 3.53)	
Information submitted by Roche for FDA/ODAC hearing	146	146	Cox regression	deaths until day 28 after end of treatment	NR	NR	HR 0.37 (0.06; 2.25)	
Coiffier 2001; Boogaerts 2003								
Boogaerts 2003	262	262	NR	NR	NR	NR	NR	
IPD data submitted by Roche 2002	262	262	IPD based hazard ratio	median observation time 85 days	8/133	8/129	HR 1.02 (0.38; 2.72)	
Roche submission 2004	262	259	Cox regression	deaths until day 28 after end of treatment	NR	NR	HR 1.02 (0.42; 2.46)	
Oberhoff 1998								
Oberhoff 1998	218	218	Proportion	during controlled treatment phase	8/114	14/104	NR	
IPD data submitted by Roche 2002	218	218	IPD based hazard ratio	median observation time 85 days	5/114	12/104	HR 0.38 (0.15; 0.99)	
Information submitted by Roche for FDA/ODAC hearing	218	218	Cox regression	deaths until day 28 after end of treatment	NR	NR	HR 0.61 (0.24; 1.55)	

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Ten Bokkel 1998								
Ten Bokkel 1998	122	120	Proportion	during study or subsequent follow up	6/87	2/33	NR	
IPD data submitted by Roche 2002	122	120	IPD based hazard ratio	median observation time 169.5 days	4/87	2/33	HR 0.80 (0.14; 4.70)	
Information submitted by Roche for FDA/ODAC hearing	122	116	Cox regression		NR	NR	HR 1.01 (0.19; 5.25)	
Österborg 1996 a, b								
Österborg 1996 a	144	144	Proportion	deaths during study period	15/47	14/49	NR	
Österborg 1996 b			Proportion		11/48		NR	
IPD data submitted by Roche 2002 (a)	144	144	IPD based hazard ratio	median observation time 168.5 days	15/47	12/49	HR 1.34 (0.55; 3.30)	
IPD data submitted by Roche 2002 (b)			IPD based hazard ratio		10/48		HR 0.78 (0.27; 2.25)	
Information submitted by Roche for FDA/ODAC hearing	144	144	Cox regression	deaths until day 28 after end of treatment	NR	NR	HR 1.02 (0.51; 2.05)	
Rose 1994								
only unpublished data (extracted from CSR by JB)*		221	Proportion	simple binary approach	11/142	4/79	1.52 (0.51; 4.53)	
Information submitted by J&J for FDA/ODAC hearing		221	Hazard ratio	double-blind study phase plus 30 days	16/142	6/79	HR 1.68 (0.66; 4.30)	

Appendix C. Evidence Tables

Table C28. KQ1 Outcome IV. Survival: Epoetin versus Control (cont'd)

study author	random	eval	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Case 1993								
unpublished data		157	Proportion	simple binary approach	10/81	9/76	1.05 (0.40; 2.73)	
Information submitted by J&J for FDA/ODAC hearing		157	Hazard ratio	double-blind study phase plus 30 days	10/81	9/76	HR 1.08 (0.44; 2.67)	
Dammacco 2001								
published and unpublished data identical		145	Proportion	simple binary approach	1/69	7/76	0.23 (0.05; 0.94)	
Information submitted by J&J for FDA/ODAC hearing		145	Hazard ratio	double-blind study phase plus 30 days	1/69	7/76	HR 0.15 (0.02; 1.20)	
Henry 1995								
only unpublished data		132	Proportion	simple binary approach	8/67	10/65	0.75 (0.28; 2.01)	
Information submitted by J&J for FDA/ODAC hearing		132	Hazard ratio	double-blind study phase plus 30 days	8/67	9/65	HR 0.86 (0.33; 2.22	

Appendix C. Evidence Tables

Table C29. KQ1 Outcome IV. Survival: Darbepoetin versus Control

study author	randomized	evaluated	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)
Vansteenkiste 2002							
Vansteenkiste 2002	320	314	unadjusted, simple Peto's Odds Ratio		22/155	19/159	NR
FDA report 2004	320	314	Cox model, adjusted for histology		65/155	78/159	HR 0.80 (0.58; 1.11)
Information submitted by industry for FDA/ODAC hearing	320	314	Cox model, adjusted for histology	median follow up 16 months	100/155	119/159	HR 0.78 (0.60; 1.01)
Hedenus 2003							
Hedenus 2003	349	344	proportion	during study or within 30 days after study	10/175	4/169	NR
Information submitted by industry for FDA/ODAC hearing	349	344	Hazard ratio; events were counted from K-M curve	median follow up 27 months	74/175	61/169	HR 1.36 (0.98; 1.90)
Kotasek 2003							
Kotasek 2003, only data from publication available		198	number of deaths at end of study reported, simple Peto's Odds Ratio calculated with RevMan	during study	7/198	3/51	HR 0.55 (0.11; 2.61)
Hedenus 2002							
Hedenus 2002, only data from publication available		66	number of deaths at end of study reported	during study	0/55	0/11	not estimable

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Table C30. KQ1 Outcome IV. Survival subgroup analysis: Epoetin versus Control

Study author	randomized	evaluated	method	follow up	events EPO (n/N), reported are deaths if not stated otherwise	events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
Littlewood 2001								
Littlewood JCO 2001, Martin et al 2003	375	375	Kaplan-Meier, unadjusted, p=0.126	26 months median f/u, 12 months after last subject completed study	155/251 (62%)	82/124 (66%)	HR 0.76 (0.58; 1.00)	lost to follow up: Epo 2, placebo 1
Littlewood 2001, hematological malignancies	173	173	Proportion	26 months median f/u	dead: 54/115	dead: 30/58	NR	lost to follow up: Epo 1, placebo 0
					alive: 60/115	alive: 28/58		
Littlewood 2001, solid tumors	202	202	Proportion	26 months median f/u	dead: 101/136	dead: 52/66	NR	lost to follow up: Epo 1, placebo 1
					alive: 34/136	alive: 13/66		
Martin et al 2003, breast cancer stage IV		55	Proportion	assumed: 26 months median f/u	dead: 22/36 (61%)	dead: 16/19 (84%)	NR, K-M curve in paper	lost to follow up: Epo 0, placebo 0
					alive: 14/36 (39%)	alive: 3/16 (16%)		

Appendix C. Evidence Tables

Table C31. KQ1 Outcome IV. Survival subgroup analysis: Darbepoetin versus Control

Study	Subgroups prospectively stratified for	Darbepo n/N	Control n/N	p-value
Hedenus 2003				
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	aggressive NHL	8/17	9/16	"similar results"
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	indolent NHL	7/20	9/29	"similar results"
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	MM	45/90	34/83	"similar results"
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	CLL	14/29	9/26	"similar results"
Vansteenkiste 2002				
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	non SCLC	K-M curve available	K-M curve available	difference between SCLC and non SCLC was not statistically significant
report submitted by pharmaceutical company for FDA/ODAC hearing May 2004	SCLC	28/47	35/45	

Appendix C. Evidence Tables

Table C32. KQ1 Outcome IV Survival: Selected characteristics of studies that reported survival outcomes and binary outcomes for survival and thromboembolic events.

Citation	Pub date	N random	Type of malig	Malignancy details	Baseline Hb	Target Hb		Standard Epo dose**	Control death rate	HR for death		RR for thrombo-embolic event	
						Lo	Hi			<1	>1	<1	>1
Case-J&J (2002)	1993	157	mixed	mixed	9.43	12.5	12.5	31,500	11.8		✓	✓	
Rose-J&J (2002)	1994	221	hematol	CLL, stage III, IV	9.2			31,500	7.6		✓		✓
Cascinu	1994	100	solid	stomach, ov, melanoma, H&N, lung, breast	8.68	10	12	31,500	0				
Cazzola-Roche (2002)	1995	146	hematol	malignant lymphoma (MM, NHL)	9.4	12.5	14	52,500	3.4	✓			
Henry	1995	132	mixed	mixed	9.5	12.5	12.5	31,500	15.4	✓		✓	
Österborg-Roche (2002)	1996	144	hematol	malignant lymphoma (MM, NHL, CLL)	8	11	15	70,000	24.5		✓		✓
Del Mastro	1997	62	solid	breast cancer, stage II	13.05	13	15	31,500	9.7	✓			
Kurz	1997	35	solid	ov, uterus, cervical ca	9.9			31,500	0				
Oberhoff-Roche (2002)	1998	218	solid	ovarian, breast, lung, GU, GI, other	9.95			35,000	11.5	✓			
Ten Bokkel-Roche (2002)	1998	120	solid	ovarian, stage II-IV	11.8			47,250	6.1		✓		✓
Thatcher, a	1999	64	solid	SCLC	13.4	13	15	33,075	4.5	✓			
Thatcher, b	1999	66	solid	SCLC	13.4			33,075	9.1		✓		✓
Dunphy	1999	30	solid	H&N, SCLC, stage III/IV	14.1			31,500	6.7	✓			
Throuvalas	2000	55	solid	cervix and bladder ca	11.3			50,000	3.7	✓			✓
Littlewood*	2001	375	mixed	NHL, MM, breast, HD, CLL, GI, other	9.8	12	15	31,500	66.1	✓			✓
Coiffier-Roche (2002)	2001	262	mixed	MM, NHL, CLL, ov, bone, GI, respir, other	9.1	12	14	31,500	6.2		✓		
Dammacco-J&J (2002)	2001	145	hematol	lymphoma (MM, NHL)	8.5			31,500	9.2	✓			✓
Österborg	2002	343	hematol	malignant lymphoma (MM, NHL, CLL)	9.25	13	14	31,500	63.0		✓		✓

Appendix C. Evidence Tables

Table C32. KQ1 Outcome IV Survival: Selected characteristics of studies that reported survival outcomes and binary outcomes for survival and thromboembolic events (cont'd)

Citation	Pub date	N random	Type of malig	Malignancy details	Baseline Hb	Target Hb		Standard Epo dose**	Control death rate	HR for death		RR for thrombo-embolic event	
						Lo	Hi			<1	>1	<1	>1
Leyland Jones*	2003	939	solid	metastatic breast cancer	12.8	10.5	14	40000	24.5		✓		✓
Henke-Roche*	2003	351	solid	H&N, stage III, IV	11.75	14	15	63000	52.0		✓		✓
Bamias	2003	144	solid	ovarian, NSCLC, SCLC,	11.5	13		30,000	5.6		✓	✓	
Machtay*	2004	141	solid	H&N non-metastatic, non resected	? 10-12	13	15	40,000	30.0		✓		✓
Witzig	2004	330	solid	lung, breast ca, other	9.45	13	15	40,000	62.8		✓		✓
N93-004*	2004	224	solid	SCLC, limited and extended disease	? >12	14	16	31,500	87.8		✓	✓	
Int-1	2004	244	solid	ovarian cancer				47,250	2.5		✓		✓
Int-3	2004	200	mixed	(no details given)				47,250	4.6		✓		✓
P-174	2004	45	hematol	CLL				31,500	8.3	✓			
Chang	2004	254	solid	breast, stage I-IV	11.25	12	14	40,000	15.2	✓			✓
EPO-CAN-15	2004	106	solid	limited disease SCLC	? >12	14		40,000	18.9		✓		✓
EPO-CAN-20	2004	62	solid	SCLC		12		40,000	64.5		✓	✓	
EPO-GBR-07*	2004	300	solid	H&N, stage I-IV	13.45	12.5	15	37,500	33.6		✓		✓
GOG-191*	2004	113	solid	cervical cancer	? >12	13		40,000	16.4	✓			✓
Vadhan-Raj	2004	59	solid	gastric or rectal cancer	13	14	15	40,000	3.2	✓			✓
Savonije	2004	315	solid	solid tumors	10.75				5.8	✓			
Razzouk	2004	222	mixed	solid tumors, Hodgkin's, non-Hodgkin's	? 10-12			42,000	1.8	✓			
O'Shaughnessy	2005	94	solid	breast ca, stages I-IIIB	13.9	13	15	40,000	0		✓		

*Study identified survival as a primary or secondary outcome.

Appendix C. Evidence Tables

Table C33. KQ1 Outcome V. Tumor Response: Epoetin versus Control

Study ID	Outcome	Response definition	Intervention (Events/sample size)	Control (Events/sample size)	Intervention: other reported measurements	Control: other reported measurements (EPO)	Relative Risk or Hazard Ratio (95% CI)	P-Value	Comments
EPO-GBR-7	Complete response at week 12	NR	108/114 (95%)	106/111 (95%)	NR	NR	NR	NR	J&J report
EPO-GBR-7	Overall response (complete and partial response) at week 12	NR	113/114 (99%)	110/111 (99%)	NR	NR	NR	NR	J&J report
N93 004 limited and extensive disease	Complete response after 3 cycles of chemotherapy (primary endpoint)	Complete response: absence of detectable tumor	18/109 (17%)	16/115 (14%)	NR	NR	NR	NS	J&J report
N93 004 limited and extensive disease	Overall response (CR plus PR) 3 cycles of chemotherapy	CR plus PR	79/109 (72%)	77/115 (67%)	Tumor response rate 73% (64%; 81%)	Tumor response rate 67% (58%; 76%)	NR	NS	J&J report
N93 004 limited and extensive SCLC	Complete response after last cycle of chemotherapy (secondary endpoint)	CR	20/109 (18%)	21/115 (18%)	NR	NR	NR	NR	J&J report
N93 004 limited and extensive SCLC	Overall response after last cycle of chemotherapy (secondary endpoint)	CR plus PR	65/109 (60%)	64/115 (56%)	NR	NR	NR	Difference (Epo minus placebo) 4 (-9; 17)	J&J report

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Table C33. KQ1 Outcome V. Tumor Response: Epoetin versus Control (cont'd)

Study ID	Outcome	Response definition	Intervention (Events/sample size)	Control (Events/sample size)	Intervention: other reported measurements	Control: other reported measurements (EPO)	Relative Risk or Hazard Ratio (95% CI)	P-Value	Comments
N93 004 extensive SCLC	Overall response (CR plus PR) 3 cycles of chemotherapy	CR plus PR	53/72	41/68			NR	Difference (Epo minus placebo) 13 (-2; 29)	J&J report
N93 004 limited SCLC	Overall response (CR plus PR) 3 cycles of chemotherapy	CR plus PR	26/37	36/47			NR	Difference (Epo minus placebo) -6 (-25; 13)	J&J report
N93 004 extensive SCLC	Overall response after last cycle of chemotherapy (secondary endpoint)	CR plus PR	38/72	35/68	Tumor response rate 53% (41%; 64%)	Tumor response rate 51% (40%; 63%)	NR	Difference (Epo minus placebo) 1 (-15; 18)	J&J report
N93 004 limited SCLC	Overall response after last cycle of chemotherapy (secondary endpoint)	CR plus PR	27/37	29/47	Tumor response rate 73% (59%; 87%)	Tumor response rate 62% (48%; 76%)	NR	Difference (Epo minus placebo) 11 (-9; 31)	J&J report
Vadhan-Raj 2004	Tumor response	no definition given	14/22	14/22	NR	NR	NR	P=0.777	Machtay 2004, "The tumour response for rectal cancer at MDACC site was similar between both treatment groups with 14/22 (63.6%) in each treatment group (p=0.777)"; Abstract, no definition for tumour response given, analysis not based on ITT population.

Appendix C. Evidence Tables

Table C33. KQ1 Outcome V. Tumor Response: Epoetin versus Control (cont'd)

Study ID	Outcome	Response definition	Intervention (Events/sample size)	Control (Events/sample size)	Intervention: other reported measurements	Control: other reported measurements (EPO)	Relative Risk or Hazard Ratio (95% CI)	P-Value	Comments
Throuvalas 2000	Complete response	WHO criteria	22/28	18/26	NR	NR	NR	NR	Throuvalas 2000 and personal communication
Machtay 2004	Complete response	no definition given	73% (52/71)	74% (52/70)	NR	NR	NR	p=0.99	Abstract slides, no definition given

Table C34. KQ1 Outcome V. Tumor Response: Darbepoetin versus Control

Study ID	Outcome	Intervention Events/sample size	Control Events/sample size	Hazard ratio (95% CI)	P value	Source & comments
Vansteenkiste 2002	Number progressed during study or follow up	94/155	110/159	1) HR 0.70 (0.53; 0.92) 2) HR 0.71 (0.54, 0.94)	NR	FDA report, 12 months median follow up; 1) Cox proportional hazard, treatment group as independent variable 2) adjusted for tumor type and region
Vansteenkiste 2002	Progression free survival (disease progression or death)	131/155	145/159	HR 0.81 (0.64; 1.03)	NR	Amgen presentation (FDA ODAC), adjusted for histology, 24 months follow up

Appendix C. Evidence Tables

Table C35. KQ1 Outcome V. Other Tumor Outcomes: Epoetin versus Control

Author	Outcome	Intervention: Events/sample size	Control: Events/sample size	Relative Risk or Hazard Ratio (95% CI)	p-value	comments
Henke 2003 Stratum I	locoregional tumor progression or death	47/102	41/94			Kaplan Meier estimate, median locoregional progression-free survival in days:EPO: 1,049d, control 1,152d; p=0.9
Henke 2003 Stratum II	locoregional tumor progression or death	30/39	16/38			Kaplan Meier estimate, median locoregional progression-free survival in days: EPO 377d, control 1,791d p=0.001
Henke 2003 Stratum III	locoregional tumor progression or death	39/39	35/39			Kaplan Meier estimate, median locoregional progression-free survival in days: EPO 141d, control 207d, p=0.006
Henke 2003	locoregional tumor progression or death	116/180	92/171	RR 1.62 (1.22; 2.14)	p = 0.0008	ITT population, adjusted for stratum and American Joint Committee on Cancer Stage, 79 and 64 pts respectively were censored. Kaplan Meier estimate, median locoregional progression-free survival in days: EPO 406d, control 745 d, p=0.04
Henke 2003	time to locoregional tumour progression and survival	NR	NR	RR 1.69 (1.16; 2.47)	P= 0.007	Full text publication, ITT population, adjusted for stratum and American Joint Committee on Cancer stage. Tumour progression was assumed when tumour size increased by more than 25%.
EPO-GBR-7	2 years disease free survival	52/56 (93%)	45/53 (85%)	NR	NR	J&J report, only 109 patients evaluated
EPO-GBR-7	3 years disease free survival	13/18 (72%)	17/21 (81%)	NR	NR	J&J report, only 39 patients evaluated

Appendix C. Evidence Tables

Table C35. KQ1 Outcome V. Other Tumor Outcomes: Epoetin versus Control (cont'd)

Author	Outcome	Intervention: Events/sample size	Control: Events/sample size	Relative Risk or Hazard Ratio (95% CI)	p-value	comments
Machtay 2004	1 year progression free survival	60% (40/67)	65% (44/68)	LR 1.10 (0.65; 1.89)	p=0.65	data taken from abstract
Machtay 2004	time to locoregional failure	29/71 (failures)	28/70 (failures)	NR	p=0.72	data taken from abstract slides
Machtay 2004	local regional failure free survival	36/71 (failures)	33/70 (failures)	NR	p=0.46	data taken from abstract slides
GOG 0191	Progression free survival, not reported when assessed	85% (49/58)	82% (45/55)	NR	NR	J&J presentation, FDA, ODAC
EPO-CAN-15	Median time to progression	467 days	419 days	NR	NR	J&J presentation, FDA, ODAC

Appendix C. Evidence Tables

Table C36. KQ1 Outcome V. Other Chemotherapy Details: Epoetin versus Control

Study	cancer details	chemotherapy category	details on therapy	duration of therapy	when and how tumor response assessed	further comments
EPO-CAN-15	limited disease SCLC	Chemo – plat all + radio, categorized as chemo_radio	"combined modality chemoradiation therapy"	not reported	not reported	
EPO-GBR-7	head and neck, stage I-IV	radiotherapy	radiotherapy with curative intent	not reported	Local tumor evidence was assessed at weeks 1,4,8 after radiotherapy and years 1, 2, 3, and 5 during follow-up	
GOG-0191	cervical carcinoma	chemo-plat all + radio, categorized as chemo_radio	concurrent radiation and cisplatin	not reported	not reported	
N93-004	SCLC, limited and extensive disease	Platinum based chemotherapy, first line therapy	etoposide plus cisplatin, no details on dosages reported	not reported	The optimal method for assessing tumor response in each patient was determined by the investigator.	TR was assessed at baseline, after the third cycle of chemotherapy, at end of study or the termination visit. The same imaging or measurement method and indicator lesions were to be used for each assessment.
Vadhan-Raj 2004, PR00-03-006	gastric or rectal ca	chemo-radio non-plat, categorized as chemo_radio	fluoropyrimidine concurrent with radiation	not reported		
Henke 2003	advanced (stage III , IV) head and neck	Radiotherapy after surgical resection, 22% (78/351) of patients radiotherapy only	60 Gy (range 56 to 64 Gy) to regions for R0 or R1; 70 Gy (range 66-74 Gy) to regions for R2 (macroscopically incompletely respected tumour) or primary definitive treatment. The spinal cord was shielded after 30-36 Gy.	Five fractions of 2.0 Gy per week or five fractions of 1.8 Gy per week.		

Appendix C. Evidence Tables

Table C36. KQ1 Outcome V. Other Chemotherapy Details: Epoetin versus Control (cont'd)

Study	cancer details	chemotherapy category	details on therapy	duration of therapy	when and how tumor response assessed	further comments
Throuvalas 2000	cervix and bladder carcinoma	Chemo – plat all + radio, categorized as chemo_radio therapy	carboplatin 90mg/m² plus radiotherapy 2 Gy/day to the pelvis	5-6 weeks	2 months post therapy and confirmed one month later	
Machtay 2004	head and neck non-metastatic, non resected	categorized as chemo_radio, but unclear if only radiotherapy	radiotherapy (66-72 Gy), unclear whether patients received also cisplatin	not reported	median follow up 12 months	

Appendix C. Evidence Tables

Table C37. KQ1 Outcome VI. Thromboembolic complications: Epoetin versus Control

Study ID						
Hb </= 10 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Cascinu 1994	0	50	0.00%	0	50	0.00%
Case J&J	2	81	2.47%	3	76	3.95%
Dammacco J&J	5	69	7.25%	1	76	1.32%
Henry J&J	6	67	8.96%	8	65	12.31%
Littlewood J&J	14	251	5.58%	5	124	4.03%
Osterborg 1996a	2	47	4.26%	0	25	0.00%
Osterborg 1996b	1	48	2.08%	0	24	0.00%
Osterborg 2002	1	170	0.59%	0	173	0.00%
Razzouk 2004	6	112	5.36%	2	110	1.82%
Rose J&J	9	142	6.34%	2	79	2.53%
Witzig J&J	9	168	5.36%	6	165	3.64%
Hb 10 to 12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
Bamias 2003	0	72	0.00%	1	72	1.39%
Chang 2005	19	175	10.86%	14	175	8.00%
Henke 2003 Roche	10	180	5.56%	6	171	3.51%
Savonije 2004	9	211	4.27%	1	104	0.96%
Ten Bokkel 1998a	2	45	4.44%	0	17	0.00%
Ten Bokkel 1998b	4	42	9.52%	0	16	0.00%
Throuvalas 2000	1	28	3.57%	0	26	0.00%
Vadhan-Raj FDA	7	29	24.14%	2	31	6.45%

Appendix C. Evidence Tables

Table C37. KQ1 Outcome VI. Thromboembolic complications: Epoetin versus Control (cont'd)

Study ID						
Hb > 12 g/dL	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
EPO-GBR-7 FDA	5	151	3.31%	1	149	0.67%
Leyland-Jones J&J	36	448	8.04%	25	456	5.48%
Machtay 2004	2	71	2.82%	0	70	0.00%
Thatcher 1999a	0	42	0.00%	0	22	0.00%
Thatcher 1999b	2	44	4.55%	0	22	0.00%
Welch 1995	1	15	6.67%	0	15	0.00%
unclear	**Treatment n**	**Treatment N**	**Percentage %**	**Control n**	**Control N**	**Percentage %**
EPO-CAN-15 FDA	16	53	30.19%	2	53	3.77%
EPO-CAN-20 J&J	1	31	3.23%	2	31	6.45%
GOG-0191 FDA	9	58	15.52%	3	55	5.45%
INT-1 J&J	3	164	1.83%	1	80	1.25%
INT-3 J&J	8	135	5.93%	1	65	1.54%
N93 004 FDA	24	109	22.02%	26	115	22.61%
P-174 J&J	0	33	0.00%	0	12	0.00%
Rosenzweig 2004	4	14	28.57%	0	13	0.00%

Appendix C. Evidence Tables

Table C38. KQ1 Outcome VI. Thromboembolism data sources: Epoetin versus Control

Study	Full text/abstract		FDA report		J&J report		Roche report		Clinical study report	
	EPO event/sample size	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**	**EPO event/sample size**	**Control event/sample size**
EPO-CAN-15	-	-	16/53	2/53	16/53	2/53	-	-		
EPO-CAN-20	-	-	"low rates in both arms"		1/31	2/31	-	-		
GBR-07	-	-	5 (3%) denominator not reported but assumed to be 151	1 (1%) denominator not reported but assumed to be 149	4/133 (n should be 151)	2/149				
GOG-191	-	-	9/58	3/55	10/58	5/55				
Henke	20/180 (including hypertension)	9/171 (including hypertension)	-	-	-	-	10/180	6/171		
Leyland-Jones	1% (5/469)	0.2% (1/470)	11/469 (death due to TE)	2/470 (death due to TE)	36/448	25/456				
Machtay	1/67, **slides: 2/71**	0/68, **slides: 0/70**	-	-	1/67	0/68	-	-		
N93004	-	-	24/109	26/115	12/109	11/115	-	-		
Witzig	8/168	5/165	-	-	9/168	6/165				
Vadhan-Raj	6/28	1/31	7/29	2/31	6/28	1/31				
Littlewood	-	-	-	-	14/251	5/124	-	-	17/251	8/124
Case	4/81	4/76			2/81	3/76				
Henry	6/67	2/65			6/67	8/65				

Appendix C. Evidence Tables

Table C39. KQ1 Outcome VII. Other adverse events -- Hypertension: Epoetin versus Control

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Hypertension
Bamias 2003	2	72	2.78%	0	72	0.00%	not reported or available from detailed results
Cascinu 1994	0	50	0.00%	0	50	0.00%	not reported or available from detailed results
Case 1993	4	81	4.94%	2	76	2.63%	not reported or available from detailed results
Dammacco 2001	3	69	4.35%	1	76	1.32%	not reported or available from detailed results
Henry 1995	2	67	2.99%	4	65	6.15%	not reported or available from detailed results
Iconomou 2003	0	61	0.00%	0	61	0.00%	not reported or available from detailed results
Kunikane 2001a	3	22	13.64%	4	17	23.53%	WHO grade ≥1; grade 1 = asymptomatic, transient ↑ >20 mm Hg or to >150/100; defined in published report
Kunikane 2001b	2	21	9.52%				
Littlewood 2001	9	251	3.59%	1	124	0.81%	not reported or available from detailed results
Osterborg 1996a	4	47	8.51%	1	49	2.04%	not reported or available from detailed results
Osterborg 1996b	5	48	10.42%				
Rosenzweig 2004	1	14	7.14%	0	13	0.00%	not reported or available from detailed results
Silvestris 1995	4	30	13.33%	0	24	0.00%	not reported or available from detailed results
Ten Bokkel 1998a	4	43	9.30%	1	28	3.57%	systolic >180 mm Hg & >30 mm ↑ from baseline or diastolic >100 mm & 15 mm ↑ from baseline; defined in published report
Ten Bokkel 1998b	7	37	18.92%				
Thatcher 1999a	2	42	4.76%	0	44	0.00%	systolic >180 mm Hg or diastolic >105 mm; from detailed results in published report; unknown whether any patients had systolic pressure >120 but <180
Thatcher 1999b	1	44	2.27%				
Welch 1995	2	15	13.33%	0	15	0.00%	systolic >140 mmHg; from detailed results in published report
Rose 1994	*86*	*142*	*60.56%*	*50*	*79*	*63.29%*	systolic >140 mm Hg or diastolic >95 mmHg; from trial sponsor's clinical study report
Alternative data							
Dammacco 2001	43	69	62.32%	36	76	47.37%	systolic >150 mmHg or diastolic >100 mmHg; data from trial sponsor's clinical study report
Rose 1994	80	142	56.34%	47	79	59.49	systolic >140 mm Hg; from trial sponsor's clinical study report
Rose 1994	6	142	4.23%	3	79	3.80%	diastolic >95 mmHg; data from trial sponsor's clinical study report

Appendix C. Evidence Tables

Table C40. KQ1 Outcome VII. Other adverse events -- Thrombocytopenia: Epoetin versus Control

Study ID	Treatment n	Treatment N	Percentage (%)	Control n	Control N	Percentage (%)
Bamias 2003	2	72	2.78%	0	72	0.00%
Boogaerts 2003	8	133	6.02%	13	129	10.08%
Cascinu 1994	0	50	0.00%	0	50	0.00%
Dammacco 2001	5	69	7.25%	5	76	6.58%
Del Mastro 1997	4	31	12.90%	4	31	12.90%
Kunikane 2001a	12	22	54.55%	3	17	17.65%
Kunikane 2001b	7	21	33.33%			
Littlewood 2001	18	251	7.17%	9	124	7.26%
Osterborg 1996a	3	47	6.38%	2	49	4.08%
Osterborg 1996b	0	48	0.00%			
Thatcher 1999a	11	42	26.19%	9	44	20.45%
Thatcher 1999b	9	44	20.45%			

Appendix C. Evidence Tables

Table C41. KQ1 Outcome VII. Other adverse events -- Rash: Epoetin versus Control

Study ID	Treatment n	Treatment N	Proportion	Control n	Control N	Proportion
Del Mastro 1997	2	31	6.45%	0	31	0.00%
Henry 1995	7	67	10.45%	2	65	3.08%
Kurz 1997	0	12	0.00%	0	12	0.00%
Osterborg 1996a	1	47	2.13%	0	49	0.00%
Osterborg 1996b	1	48	2.08%	0		
Thatcher 1999a	5	42	11.90%	4	44	9.09%
Thatcher 1999b	1	44	2.27%			
Welch 1995	1	15	6.67%	0	15	0.00%

Table C42. KQ1 Outcome VII. Other adverse events -- Seizures: Epoetin versus Control

Study ID	Treatment n	Treatment N	Proportion	Control n	Control N	Proportion
Cascinu 1994	0	50	0.00%	0	50	0.00%
Case 1993	2	81	2.47%	2	76	2.63%
Henry 1995	3	67	4.48%	2	65	3.08%

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison I. Different Weight-Based Doses											
Kunikane 2001	72 Evaluable: A) 16 B) 18 0: 19	Epoetin beta	A) 100 IU/Kg tiw B) 200 IU/kg tiw	Placebo	Weight	8	Stopping: if Hb >16 g/L (men) or >14 g/dl (women) drug was stopped	NR	NR	Full-text	Hb, Transfusions
Ten Bokkel 1998	122 A) 45 B) 42 o) 33	Epoetin beta	A) 150 IU/kg tiw B) 300 IU/kg tiw	No Placebo	Weight	Through duration of chemo plus 3-24 weeks depending duration of chemo	Decreasing: if Hb increased ≥2 g/dl dose was reduced by 50%. If Hb level >15g/dl. Drug stopped until Hb <14g/dl	As necessary	Usually if Hb < 9.7 g/dl	Full-text, unpublished	RBCT, TR, AE
Thatcher 1999	130 A) 44 B) 42 o) 44	Epoetin alfa	A) 150 IU/kg tiw B) 300 IU/kg tiw	No Placebo	Weight	26	Decreasing: if Hb exceeded 15 g/dl Drug stopped and restarted with 50% if Hb <13 g/dl.	As necessary	Usually if Hb ≤ 10 g/dl	Full-text, unpublished	Hb, RBCT, QoL, AE
Glaspy 2002	160 A) 33 B) 31 C) 32 D) 32 Epo: 32	Darbepoetin alfa	A) 3,0 µg/kg Q2W B) 5,0 µg/kg Q2W C) 7,0 µg/kg Q2W D) 9,0 µg/kg Q2W	40000 iU Epo alfa	Darb weight based, Epoetin fixed	12	Only Epoetin Increasing: if Hb increase < 1.0 g/dl at wk 6 EPO increased to 60,000 IU QW	NR	NR	Full-text	Hb response, Hb change, transfusions, QoL, Safety , Antibodies

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison I. Different Weight-Based Doses (cont'd)											
Hedenus 2002	66 A) 11 B) 22 C) 22 O: 11	Darbepoetin	A) 1.0 µg/kg QW B) 2.25 µg/kg QW C) 4.5 µg/kg QW	Placebo	Weight	12	Decreasing: if Hb increase >2 g/dl in 4 wks drug reduced by 50%, if Hb level >15 g/dl (men) or 14 g/dl (women) drug stopped and reinstated at 50% if Hb <13 g/dl	As necessary	Hb <8g/dL	Full-text	Dose response Hb response, Hb change, RBC transfusion
Kotasek 2003	259 A) 32 B) 17 C) 46 D) 28 E) 35 F) 40 O: 51	Darbepoetin	A) 4.5 µg/kg Q3W B) 6.75 µg/kg Q3W C) 9 µg/kg Q3W D) 12 µg/kg Q3W E) 13.5 µg/kg Q3W F) 15 µg/kg Q3W	Placebo	Weight	12	Increasing not allowed, decreasing: if Hb increased >15 g/dl (men) or >14 g/dl (women) drug stopped and reinstated at a lower dose level if Hb <13 g/dl	NR	NR	Full-text	Hb response, Hb change, transfusions, QoL, Safety, Antibodies

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison II. Different Fixed Doses											
Cazzola 1995	146 Treatment: A) 31 B) 29 C) 31 D) 26 0: 29	Epoetin beta	A) 1000 daily B) 2000 daily C) 5000 daily D) 10000 daily	No treatment	Fix	8	Decreasing: if Hb increased >2 g/dl OR Hb level >12.5 g/dl dose was reduced from 7x to 3x per week. If Hb >13 g/dl (MM) or >15 g/dl (NHL) drug was stopped	If serum iron or transferrin saturation below normal limit => Iron (oral)	At discretion of physician	Full-text	HR, Hb, RBCT, AE
Glimelius 1998	84 A) 41 B) 43	Epoetin alfa	10000 tiw	2000 tiw	FIX	18	Not allowed. Stop if Hb > 14,5 g/dl	As Necessary	If Hb < 8,5 mg/dl at discretion of physician	Full-text	Increase Baseline HB Level (Response defined as increase over baseline by greater than 1 g/dl. Failure decrease >1 g/dl) or need of RBC transfusions Safety QoL
Johansson 2001	180 A) 90 B) 90	Epoetin beta	5000 tiw	1000 tiw	FIX	12	Dose doubled in high dose group if Hb increased<1,5 after week4 or <2 after week8. In both if Hb >14 treatment withdrawn until Hb <13. Then twice a week.	Fix 200 mg/d oral	By investigators physicians	Paper	Hb Response defined as increase ≥ 1,5 g/dl and also ≥2 g/dl. Hb level (after w 4/8/12) Patients required Transfusion Transfused Volume Adverse events / Safety QoL (EORTC QoL30)

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison II. Different Fixed Doses (cont'd)											
Ollson 2002	180 A) 90 B) 90	Epoetin beta	5000 tiw.	1000 tiw	FIX	24	Increase in high dose group if Hb increased<1 g/dl after week4 or <2 after week8. In both if H >15 treatment withdrawn until Hb <14. Then twice a week. If Hb >14 D. twice /w	Regardless S-ferritin - 200-mg/d oral.	By investigators physicians	Paper	Hb Response defined as increase ≥ 2 g/dl ;also for I > 1g/dl. Hb mean level (after w 4/8/12/16/20/24) Need for transfusion Safety QoL (EORTC QoL30)
Sakai 2004	86 A) 28 B) 29 C) 29	Epoetin beta	A) 9000 QW B) 18000 QW C) 36000.QW	No placebo	FIX	12	Withheld if Hb >14g/dl (restarted if Hb <12)	Oral fix	NR	Abstract	Increase in Hb concentration at last evaluation Percentage Hb > 2/gdl Transfusion requirements Adverse effects QoL (Fact- An)

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens											
Granetto 2003	546 A) 268 B) 264	Epoetin alfa	10000 tiw (If patient weight: <45 kg => 5000 tiw, if >100kg => 15000 tiw)	150/ kg tiw	FIX vs. weight	12	I: Double Dose after 1st chemotherapy Hb increase <1 or Reticulocyte <40000/µl D) by 25% if Hb increase ≥2/m Stop by Hb >14 until <12 than reinstated with 75 % Dose.	If transferrin saturation < 20%	Hb < 8g/dl	Paper	Transfusion (RBC or whole blood) requirements over days 29-84 (proportion of pt) Change in Hb Level from baseline Proportion of patients who responded to Epoetin (complete if Hb ≥2 g/dl without transfusion after 4 w; partial HB change 0-2 g7dl without transfusion 4w) CLAS / LASA
Hesketh 2004	243	Darbep oetin	325 µg Q1W	4,5 µg /kg Q1W	FIX vs. weight	16	After correction of Anemia ≥12 g/dl reduction to Q3W = Maintain Phase Therapy withheld if Hb>15(men) or >14(women) Reinstated with 200µg / 3µg/kg if Hb <13.	By investigat ors physicians	By investigators physicians Recommenda tion Hb < 8g/dl	Paper	Hem. response defined as increase ≥ 2 g/dl or a concentration ≥ 12 g/dl in absence of RBC transfusion within previous 28 d Time required to achieve Hb Response Transfusion (RBC) requirements from week 5 (proportion of pt) RBC units Safety

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison IV. More- versus Less-Frequent Dosing											
Cazzola 2003	241 A) 119 B) 122	Epoetin beta	30000 QW	10000 tiw	FIX	16	Double Dose if Hb Increase ≤ 0,5 g/dl. After week 4 or RBCT. Decrease (50%Dose) if Hb Increase ≥2 g/dl. Stop if Hb >14 reinstated with 50% reduced Dose if Hb <13.	Iron (I.V.) if transferrin saturation < 20%.	If necessary Hb< 8,5g/dl	Paper	Time-adjusted Hb between w5 and w16 (Hb AUC) if HRBC transfused adjusted results obtained. Hb Response ≥2 g/dl vs. baseline without transfusion Portion of pat correct anemia ≥11 or ≥12 Severe anemia ≥8, 5 Transfusion free Transfusion requirements Survival Adverse effects
Steensma 2005	365 A) 183 B) 182	Epoetin	After period of fix treatment with 3 x 40000 IU Epo then 120000 Epo Q3W	After period of fix treatment with 3 x 40000 IU continuing Epo 40000 Epo QW	FIX	21 weeks (incl 3 week same qw treatment)	NR	325 mg oral qw FIX	NR	Abstract	Proportion of pts requiring transfusion. Hb increment from baseline= Response ≥2 g/dl and ≥ 3g/dl vs. baseline Final Hb Survival adverse effects

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Intervention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison V. Front-Loaded versus Reduced or Constant Dosing											
Glaspy 2003	127: A)32 B)32 C)32 Epo:31	Darbepoetin (control Epoetin)	A) 4.5 µg/kg/w until Hb > 12 g/dl, then 1.5 µg/kg/wk up to week 12 B) 4.5 µg/kg/w, then 8 x 2.25 µg/kg/w C) 4 x 4.5 µg/kg/w, then 8 x 3 µg/kg/Q2W	40000 iU Epo alfa	Darbepo weight based, Epoetin fixed	12	For Darbepo: Withheld if Hb level > 15.0 g/dl (m) or 14 g/dl (w); If Hb < 13 g/dl drug reinstated at 75% Dose. Control (Epo) increasing: if Hb increase < 1.0 g/dl at week 4 EPO increased to 60,000 IU QW	NR	Hb≤8 g/dl	Full-text	Mean change in Hb level Proportion of patients with Hb response ≥2 g/dl vs. baseline without transfusion last 6 weeks Time to Hb response Safety (sum Adverse Events) QoL (FACT-F)
Kotasek 2004	727 A) 356 B) 367	Darbepoetin	4,5 µg/ kg QW (week 1-4) Q3W (week 5-16)	2,25 µg/ kg QW	Weight	16	Only in Control If Hb response week 6 < 1/gdl or RBC Transfusion dose Doubled.	NR	NR	Abstract (Poster)	Red blood cell transfusion (from Week 5 to end of treatment) or withdrawal from study during the 16-week treatment period (aside from death and disease progression) Proportion of patients receiving transfusion during treatment phase. Time to Hb response Increase in Hb level ≥ 2 g/dl from baseline Safety

Appendix C. Evidence Tables

Table C43. KQ2: Study Characteristics, Part I (cont'd)

study author	participants randomized	Drug	Intervention (Early)	Control Late	weight based or fix	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
KQ2 Comparison VI. Titrated versus Constant Dosing											
Österborg 1996	144 A) 47 B) 48 o) 49	Epoetin beta	A) Fix 10000 iU Q7W B) Titration: Stat Dose 2000 iU (for 8w) if then Hb<11g /dl =>5000 Q7W; if week 12 Hb<11 g/dl => 10000 (Q7W)	No Placebo	FIX / vs. Titration	24	If Hb > 13 (women) or 14 (men) dose stopped until Hb decrease < 1 g/dl than restarted at reduced frequency. Non responders (Pt with transfusion need after 12w therapy with 10000 Dose) withdrawn	NR	Hb < 10 g/dl	Full-text Unpublished	HR, Hb, RBCT, AE
KQ2 Comparison VII. Intravenous versus Subcutaneous Dosing											
Justice 2005	120 A) 59 B) 59	Darbepoetin alfa	4,5mcg/kg intravenous QW until week6 then Q3W	4, 5mcg/kg subcutaneous QW until week6 then Q3W	Weight	18	Withheld if Hb ≥ 14g/dl (women) 15 (men), reinstated Q3W if HB ≤13g/dl.	At discretion of investigator or study center	If Hb < 8 g/dl or if symptoms of anemia present	Full-text	Hem. Response HB≥12 g/dl or I ≥2 g/dl Reaching Hb Target 11 g/dl Mean change Hb RBC Transfusions Safety

Appendix C. Evidence Tables

Table C44. KQ2: Study Characteristics, Part II

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
KQ2 Comparison I. Different Weight-Based Doses											
Kunikane 2001	72	Lung	Solid	Platinum based chemotherapy	Hb 9.0-13 g/dl	A) 12,3 (SD1,2) B) 12,3 (SD1,4)	12,0 (SD 0,9)	12	A) 62,7 (SD 8,7) B) 62,7 (SD 4,8)	59,5 (SD 9,9)	Adults
Ten Bokkel 1998	122	ovarian, stage II-IV	Solid	Platinum based chemotherapy	Hb ≤ 13gdl	Median / Range A) 12.0 (11.3-12.6) B)11.6 (10.5-12.2)	Median / Range 11.8 (10.6-12.5)	A10-12	A) 58.51 B) 60,97	58.83	Adults
Thatcher 1999	130	SCLC	solid	Platinum based chemotherapy (89% of patients)*	Hb > 10.5 g/dl	A) 13.4 (SD 1.3)* B) 13.5 (SD 1.3)*	13.4 (SD 1.3)*	12	A) 59 (43-72 B) 58.5 (30-72)	60 (39-74)	Adults
Glaspy 2002	160	Breast, GI, lung, other	Solid	Chemotherapy	Hb <11 g/dl	9.82 (SD 0.95) 9.8 (SD 1,0) For (A-D reported)	9.73 (SD 1.17) 9,7 (1,2)	10	64.3 (SD 12.0) For (A-D reported)	63.9 (SD 12.3)	Adults

Appendix C. Evidence Tables

Table C44. KQ2: Study Characteristics, Part II (cont'd)

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
KQ2 Comparison I. Different Weight-Based Doses (cont'd)											
Hedenus 2002	66	Malignant lymphoma (HD, NHL, CLL, MM)	Hematological	Chemotherapy	Hb ≤11.0 g/dl	A) 9,74 (SD 0,82) B) 9,4 (SD 1,25) C) 9,7 (SD 0,85)	9.54 (SD 0,95)	10	Median / Range A) 63 (25-80) B) 64 (26-80) C) 70 (52-84)	Median 63 (25-80)	Adults
Kotasek 2003	259	Breast, gyne, gastrointestinal, lung, other	Solid	Chemotherapy, not reported if with or without platinum, interpreted as some platinum)	Hb ≤11.0 g/dl	9.93 (SD 1.0) (Reported for A-F, F slightly higher 10,4)	9.87 (SD 1.12)	10	58.3 (SD 11.9)	56,2 (SD 12,4)	Adults
KQ2 Comparison II. Different Fixed Doses											
Cazzola 1995	146	Malignant lymphoma (MM, NHL)	Hematological	Chemotherapy	Hb ≤11 g/dl independent of transfusion	A) 9,3 (SD 0,9) B) 9,4 (SD 0,9) C) 9.4 (SD 1.2) D) 9.4 (SD 1.0)	9.5 (SD 1.1)	10	A) Median 67 (48-82) B) Median 65 (40-82) C) Median 68 (42-85) D) median 63 (28-80)	Median 68 (28-80)	Adults
Glimelius 1998	83	Gastric 20 Pancreatic 10 Biliary 6 Colon 48	Solid	Chemotherapy	m <13 g/dl w<11,5 g/dl	10,9 (1,0)	10,8 (1,0)	10-12	Mean 61 31-78	Mean 61 34-79	Adults
Johansson 2001	180	Hormone refractory prostate cancer	Solid	Mixed (antitumor not further stated)	Hb ≤ <10,5g/dl	9,1 (+- 0,9)	9,2 (+- 0,8)	10	Mean 71 (+- 8)	Mean 72 (+- 7)	Categorized as Elderly
Ollson 2002	180	Metastatic breast cancer	Solid	Mixed	Hb ≤ <11,0g/dl	9,8 (Range 6,4 – 11,0)	9,9 (Range 7,7 – 11,1)	10	57 (range 35– 83)	58 (Range 30-82)	Adults
Sakai 2004	86	Lung cancer Malignant Lymphoma	Mixed	Chemotherapy	Hb ≤ <11,0g/dl	NR	NR	10	A) 60,5 B) 63,0 C) 61,9	NR	Adults

Appendix C. Evidence Tables

Table C44. KQ2: Study Characteristics, Part II (cont'd)

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens											
Granetto 2003	546	Lung: 33,3%/33,3% Gynecological: 29,4%/31,8% Other: 37,3%/34,9%	Solid	Chemotherapy (platinum)	Hb ≤ 10,5 g/dl or on chemotherapy Hb ≥ 12 with but ≥ 10,5 chemotherapy following decrease ≥1, 5	9,61 (1,02)	9,65 (1,05)	10	Mean 61,8 (SD 10,5)	Mean 61,1 (SD 10,0)	Adults
Hesketh 2004	243	Breast GIT Genitourinary Gynecologic Lung Lymphoproliferative	Mixed	Chemotherapy	Hb ≤ 11g/dl	10,2 (SD 1,0)	10,2 (SD 0,9)	A10-12	Mean 63,2 (SD 13,3)	Mean 60,4 (SD 13,3)	Adults
KQ2 Comparison IV. More- versus Less-Frequent Dosing											
Cazzola 2003	241	MM NHL CLL	Hematological	Chemotherapy	9-11 g/dl	10,2 (1,0)	10,1 (1,0)	10	38-82 Median 67	33-90 Median 65	Adults
Steensma 2005	365	NR (Pts eligible if they need not to be receiving active anti-neoplastic therapy)	unclear	89 % of pts receiving anti-neoplastic therapy. Type unclear	Men <12 g/dl; women <11g/dl	NR	NR	unclear	NR	NR	unclear

Appendix C. Evidence Tables

Table C44. KQ2: Study Characteristics, Part II (cont'd)

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
KQ2 Comparison V. Front-Loaded versus Reduced or Constant Dosing											
Glaspy 2003	127	Breast GiT Lung Others	Solid	Chemotherapy	Hb ≤11 g/dl	A) 9,54 (SD1, 12) B) 9,90(SD1, 02) C) 9,90 (SD0, 99)	Epoetin: 9,84 (SD 0,83)	10	A) 60,5 (SD 14,1) B) 66,4 (SD 12,7) C) 62,7 (SD 13,2)	Epoetin: 63,5 (SD 8,7)	Adults
Kotasek 2004	727	Hematological Lung Breast Other solid	Mixed	Chemotherapy	Hb ≤ <11,0g/dl	9,6 (SD1,0)	9,6 (SD1,0)	10	61,0 (SD13,0)	61,9 (12,8)	Adults
KQ2 Comparison VI. Titrated versus Constant Dosing											
Österborg 1996	144	malignant lymphoma (MM, NHL, CLL)	Hematological	Chemotherapy	Hb ≤ 10gdl	A) median 8.0 (range 6.2-10.1) B) median 8.0 (range 5.5-10.3)	median 8.1 (range 5.2-9.8)	10	66(43-84) 65 (38-82)	64 (36-83)	Adults
KQ2 Comparison VII. Intravenous versus Subcutaneous Dosing											
Justice 2005	120	Lung Breast Gastrointestinal Gynecological Myeloproliferative Other	Mixed	Chemotherapy (50% Platinum)	Hb ≤≤11 g/dl	9,5(SD0,8)	9,6 (SD 0,9)	10	63,9 (SD13,6)	63,1 (SD12,6)	Adults

Appendix C. Evidence Tables

Table C45. KQ2: Study Quality

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality
KQ2 Comparison I. Different Weight-Based Doses							
Kunikane 2001	yes	yes (central randomization service)	double blind	no placebo	no	yes	low
Ten Bokkel 1998	yes	yes	open label	no placebo	ITT or 10%	yes	low
Thatcher 1999	unclear	unclear	open label	no placebo	ITT	yes	low
Glaspy 2002	unclear	unclear	no	no placebo	ITT or 10%	yes	low
Hedenus 2002	yes	yes (central randomization service)	double blind	placebo	ITT	yes	high
Kotasek 2003	unclear	unclear	double blind	placebo	yes for safety, not sure for transfusion	Yes (Except a slightly higher proportion of patients in the 12 µg group had breast cancer (61%) compared with the other groups, which ranged from 15 to 38%. I 12 µg group had also a slightly higher mean Hb at baseline (10.4 g/d, compared with the other groups (9.7 to 10.2).	high

Appendix C. Evidence Tables

Table C45. KQ2: Study Quality (cont'd)

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality
KQ2 Comparison II. Different Fixed Doses							
Cazzola 1995	yes	unclear	no	no placebo	ITT or 10%	yes	low
Glimelius 1998	yes	unclear	no	no	ITT	yes	low
Johansson 2001	unclear	unclear	open label	no	*ITT*	yes	low
Ollson 2002	yes	yes	open label	no	*ITT > 10%*	yes	low
Sakai 2004	unclear	unclear	double blind	no	> 10 %	yes (except reduced serum Epo concentration in 36000 Group. Double serum ferritin in 9000 Group	low
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens							
Granetto 2003	unclear	unclear	double blind	no	ITT or > 10 %	yes	low
Hesketh 2004	yes	unclear	no	no	*ITT or 10 %*	Yes (at baseline) Therapy decisions about Fe / RBC not reported	low
KQ2 Comparison IV. More- versus Less-Frequent Dosing							
Cazzola 2003	unclear	unclear	no	no	ITT	yes	low
Steensma 2005	unclear	unclear	No	No	unclear	unclear	low
KQ2 Comparison V. Front-Loaded versus Reduced or Constant Dosing							
Glaspy 2003	unclear	unclear	no	No placebo	ITT or 10%	yes	low
Kotasek 2004	unclear	unclear	double blind	yes (for schedule)	*ITT*	yes	low
KQ2 Comparison VI. Titrated versus Constant Dosing							
Österborg 1996	yes	yes	no	no	ITT	yes	low
KQ2 Comparison VII. Intravenous versus Subcutaneous Dosing							
Justice 2005	yes	unclear	open label	no	ITT or <10%	yes	low

Appendix C. Evidence Tables

Table C46. KQ2: Hematologic Response

study author	Hb response definition	Early (n)	Early (N)	Percentage (%)	Late (n)	Late (N)	Percentage (%)	Comments
KQ2 Comparison I. Different Weight-Based Doses								
Glaspy 2002 Group A	Hb increase of 2 g/dl independent of transfusion in the previous 28 days	20	33	60.61%	*19*	*32*	59.38%	A) 3 µg/kg Q2W Darb, K-M percentages 60% (39; 80), EPO: 60% (40; 79)
Glaspy 2002 Group B		25	31	80.65%				B) 5 µg/kg Q2W Darb, K-M percentages 79% (56; 100)
Glaspy 2002 Group C		18	32	56.25%				C) 7 µg/kg Q2W Darb, K-M percentages taken from figure: 55%
Glaspy 2002 Group D		21	32	65.63%				D) 9 µg/kg Q2W Darb, K-M percentages taken from figure: 67%
Hedenus 2002 Group A	Hb increase of 2 g/dL independent of transfusion in the previous 28 days	5	11	45.45%	*1*	*11*	9.09%	Absolute numbers were derived using Kaplan-Meier method; A) 45% N=11, control 10%, N=11
Hedenus 2002 Group B		12	22	54.55%				B) 55%, N=22
Hedenus 2002 Group C		14	22	63.64%				C) 62%, N=22
Kotasek 2003 Group A	Increase ≥ 2 g/dl from baseline, in absence of previous RBCT in previous 28 d	8	32	25.00%	7	51	13.73%	Derived using Kaplan-Meier method; arm A) 24%, N=32, control 14%, N=51
Kotasek 2003 Group B		8	17	47.06%				B) 48%, N=17
Kotasek 2003 Group C		23	46	50.00%				C) 50%, N=46
Kotasek 2003 Group D		17	28	60.71%				D) 62%, N=28
Kotasek 2003 Group E		20	35	57.14%				E) 58%, N=35
Kotasek 2003 Group F		20	40	50.00%				F) 50%, N=40

Appendix C. Evidence Tables

Table C46. KQ2: Hematologic Response (cont'd)

study author	Hb response definition	Early (n)	Early (N)	Percentage (%)	Late (n)	Late (N)	Percentage (%)	Comments
KQ2 Comparison II. Different Fixed Doses								
Cazzola 1995 Group A	Hb increase of 2 g/dl independent of transfusion	2	31	6.45	*2*	*29*	*7,4 (6,89)*	Only % reported
Cazzola 1995 Group B		9	29	31.03				Only % reported
Cazzola 1995 Group C		19	31	61,29)				Only% reported
Cazzola 1995 Group D		16	26	61.54				Only % reported
Glimelius 1998	Hb Response ≥2 g/dl vs. baseline without transfusion	26	41	63.41	11	43	25.58	
Johansson 2001	HB Response defined as increase ≥ 2 g/dl	39	90	43.33	23	90	25.56	% reported also after week (4/ /8). At week 12 P<0,05
Ollson 2002	HB Response defined as increase ≥ 2 g/dl	53	90	58.88	46	90	51.11	Estimated from Fig3 (Proportion after 24 week)
Sakai 2004 Group A	HB Response defined as increase ≥ 2 g/dl	9	22	40.9				Observation period and independence of transfusion not stated.
Sakai 2004 Group B		16	24	66.66				
Sakai 2004 Group C		18	23	78.26				
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens								
Granetto 2003	Complete if increase of Hb ≥2 g/dl without transfusion after 4 w	110	218	50.46	122	230	53.04	22 pt excluded from efficacy evaluation in cause of protocol violations % as reported P0,040; Mantel Hanzel X Test
KQ2 Comparison IV. More- versus Less-Frequent Dosing								
Cazzola 2003	Hb Response ≥2 g/dl vs. baseline without transfusion	85	118	72.03	89	119	74.78	% reported.
Steensma 2005	Hb Increment ≥2 g/dl vs. baseline	109	182	59.89	128	183	69.95	% reported for 2 g/dl Hb increment P = 0.04 with or without transfusion not reported
KQ2 Comparison V Front-Loaded versus Reduced or Constant Dosing								
Glaspy 2003 Group A	Hb increase of 2 g/dl independent of transfusion	19	32	59.38	*15*	*30*	*50*	Only % reported
Glaspy 2003 Group B		17	30	56.67				Only % reported
Glaspy 2003 Group C		20	30	66.67				Only% reported
KQ2 Comparison VI. Titrated versus Constant Dosing								
Österborg 1996 Group A	Hb increase of 2 g/dl (Mean over 4 weeks and independence of erythrocyte transfusions during 8 weeks period)	21	44	44.68	*8*	*39*	*16.33*	Dose FIX
Österborg 1996 Group B		23	38	44.92				Dose Titration

Appendix C. Evidence Tables

Table C47. KQ2: Studies Not Included for Hematologic Response

study author	Hb response definition	Intervention n	Intervention N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Hesketh 2004	HB Response defined as increase ≥ 2 g/dl or a concentration ≥ 12 g/dl in albescence of RBC transfusion within previous 28 d	10	122	86 (CI 78-94)	101	120	84 (CI 76-92)	KM – estimate Difference in Percentages 2 (CI –8-12)
Justice 2005	HB response HB≥12 g/dl or I ≥2 g/dl	40	59	67.78	47	59	79.66	Estimated by Kaplan Meier method % reported: A 80 (67 to 92) B) 68 (52 to 83)

Additional Data

study author	Hb response definition	Intervention n	Intervention N	Proportion (%)	Control n	Control N	Proportion (%)	Comments
Granetto 2003	Complete if increase of Hb ≥2 g/dl without transfusion after 4 w	58	105	55.24	60	113	53.09	Weight 45-63 kg
Granetto 2003		32	66	48.48	38	70	54.28	Weight 70 –100 kg

Appendix C. Evidence Tables

Table C48. KQ2: Transfusion Studies

Study ID	Intervention (n)	Intervention (N)	Percentage (%)	Control (n)	Control(N)	Percentage (%)	Comments
KQ2 Comparison I. Different Weight-Based Doses							
Kunikane 2001 Group A	1	16	6.25	0	19		
Kunikane 2001 Group B	2	18	11.11				
Ten Bokkel 1998 Group A	2	45	4.44	13	33	39.39	
Ten Bokkel 1998 Group B	6	42	14.29				
Thatcher 1999 Group A	19	42	45.24	26	44	59.09	Total number of transfusion significant difference between Group A / B
Thatcher 1999 Group B	9	44	20.45				
Glaspy 2002 Group A	1	30	3.33%	11	30	36.67%	K-M percentages reported, A) 4% (0; 11), EPO-control 36% (10; 87)
Glaspy 2002 Group B	7	30	23.33%				B) 22% (6; 37)
Glaspy 2002 Group C	7	30	23.33%				C) 23% (7; 30)
Glaspy 2002 Group D	3	29	10.34%				D) 11% (0; 23)
Hedenus 2002 Group A	3	11	27.27%	5	11	45.45%	Excluding first 4 weeks, counting week 5 to end of treatment derived from K-M estimates, arm A) 27% (95% CI 1-54), N=11, control: 45% (16-75), N=11
Hedenus 2002 Group B	6	22	27.27%				27% (9-46), N=22
Hedenus 2002 Group C	3	22	13.64%				15% (0-30), N=22

Appendix C. Evidence Tables

Table C48. KQ2: Transfusion Studies (cont'd)

Study ID	Intervention (n)	Intervention (N)	Percentage (%)	Control (n)	Control(N)	Percentage (%)	Comments
KQ2 Comparison I. Different Weight-Based Doses (cont'd)							
Kotasek 2003 Group A	8	30	26.67%	23	50	46	arm A) 25% (9%-41%), N=30; control 46% (32%-61%), N=50
Kotasek 2003 Group B	5	17	29.41%				arm B) 28% (7%-51%), N=17
Kotasek 2003 Group C	12	41	29.27%				arm C) 30% (16%-44%), N=41
Kotasek 2003 Group D	7	27	25.93%				arm D) 26% (7.5%-41%), N=27
Kotasek 2003 Group E	9	35	25.71%				arm E) 27% (11%-40%), N=35
Kotasek 2003 Group F	7	38	18.42%				arm F 19% (6%-32%), N=38
KQ2 Comparison II. Different Fixed Doses							
Cazzola 1995 Group A	7	31	22.58	*Placebo 8*	*Placebo 29*	*27.59*	
Cazzola 1995 Group B	5	29	17.24				
Cazzola 1995 Group C	6	31	19.35				
Cazzola 1995 Group D	4	26	15.38				
Glimelius 1998	3	41	7.32	5	43	11.63	not significant
Johansson 2001	36	90	40.00%	49	90	54.44%	
Ollson 2002	30	90	33.33	32	90	35.66	% reported
Sakai 2004 Group A	5	22	22.72				
Sakai 2004 Group B	4	24	16.66				
Sakai 2004 Group C	0	23	0				
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens							
Granetto 2003	37	225	16.44	30	238	12.61	Only 463 of 546 patients assed (drop outs in first 4 weeks). Transfusion free % reported - -Kaplan Meier Estimate Log rank p=0,32% RR 1,29 (CI 0,78-2,14)
Hesketh 2004	23	122	18.88	19	120	15.83	Reported: Fix: 19% (CI:11-27) W: 16% (CI 9-23)

Appendix C. Evidence Tables

Table C48. KQ2: Transfusion Studies (cont'd)

Study ID	Intervention (n)	Intervention (N)	Percentage (%)	Control (n)	Control(N)	Percentage (%)	Comments
KQ2 Comparison IV. More- versus Less-Frequent Dosing							
Cazzola 2003	10	115	9.24	16	114	14.03	Additional source ASH 2002 Mean Hb in both groups before transfusion 7,4 g/dl P=0,14 Cochrane M.-Haenzel Test adjusted for underlying disease
Steensma 2005	29	182	15.93	35	183	19.13	% reported; P= 0.51
KQ2 Comparison V. Front-Loaded versus Reduced or Constant Dosing							
Kotasek 2004	89	356	25.00%	88	367	23.98	Week 5 to end of treatment estimate from reported %. A) 24% (CI 19 ; 28); B) 25% (CI 20 ; 30)
KQ2 Comparison VI. Titrated versus Constant Dosing							
Österborg 1996 Group A	27	47	56.25	40	49	81.6	% of transfused patients during m 2 to 6 reported
Österborg 1996 Group B	31	48	64.58				
KQ2 Comparison VII. Intravenous versus Subcutaneous Dosing							
Justice 2005	21	59	35.59	19	59	32.2	% reported for week 5 up to end. A)32 (CI 18 ; 45) B) 35 (CI 20 ; 50)

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Table C49. KQ2: Overall Survival

Study author	Randomized	Evaluated	Method	Follow up	Events INTERVENTION (n/N), reported are deaths if not stated otherwise	Events control (n/N), reported are deaths if not stated otherwise	HR (95% CI)	Comments
KQ2 Comparison I. Different Weight-Based Doses								
Ten Bokkel 1998 Group A	45		Proportion	During study or subsequent follow up	1 / 45	2 / 33		
Ten Bokkel 1998 Group B	42				3 /42			
Thatcher 1999 Group A			Proportion		1 / 42	3 / 44		
Thatcher 1999 Group B					5 /44			
KQ2 Comparison II. Different Fixed Doses								
Cazzola 1995	146	146	Proportion	NR	4/117	2 / 029	NR	In Full text deaths not reported for the different intervention Groups
Glimelius 1998								Death or terminal disease reported
Ollson 2002	180		Proportion	24 week	21	19		
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens								
Granetto 2003	268 / 264	255 / 255	Proportion		20 / 268	14 / 264		Not based on Kaplan-Meier estimate
Hesketh 2004	243		Proportion	19 week	13/122	11/120		Study + 30d observed.
KQ2 Comparison IV. More-versus Less-Frequent Dosing								
Steensma 2005	NR	NR	NR	NR	NR	NR	NR	Only reported slight trend towards the intervention group (120k) p=0,10.
KQ2 Comparison VII. Intravenous versus Subcutaneous Dosing								
Justice 2005	120	118	Proportion	18 w + 30d after	7/59	5/59		

Appendix C. Evidence Tables

Table C50. KQ2: Thrombotic Events

Study ID	Intervention n	Intervention N	Percentage (%)	Control n	Control N	Percentage (%)	Definition of TE	Comments
KQ2 Comparison I. Different Weight-Based Doses								
Ten Bokkel 1998 Group A	2	45	4.44%	0	31	0.00%	Cardiovascular events	
Ten Bokkel 1998 Group B	4	42	9.52%	0		0.00%		
KQ2 Comparison II. Different Fixed Doses								
Glimelius 1998	6	41	13.95	3	43	7.32	NR	! Deep VT and 1cerebral ischemic attack reported.
Johansson 2001	11	90	12.22	4	90	4.44	Cardiovascular events	Deep VT 4/1; Mi 2/0; Heart failure 2/1; Atrial fibrillation 1/1; Cerebral bleeding 2/2
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens								
Granetto 2003	5	268	1.9	5	264	1.9	No	Only AE related to study drug reported.
KQ2 Comparison IV. More-versus Less-Frequent Dosing								
Cazzola 2003	18	118	15.25	21	119	17.65	Vascular disorders	Part % reported. Recalculated from 85 patients reported adverse events in each group.
KQ2 Comparison VI. Titrated versus Constant Dosing								
Österborg 1996 Group A	1	47	2.13	0	49	0	Pulmonary Embolism	
Österborg 1996 Group B	2	48	4.17					

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Table C51. KQ2: Rash

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Rash	Comments
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens								
Granetto 2003	5	268	1.9	1	264	0.4	Skin reactions (incl. pruritus)	Only AE related to study drug reported.
KQ2 Comparison VI. Titrated versus Constant Dosing								
Österborg 1996 Group A	1	47	2.13	0	49	0		Dose FIX
Österborg 1996 Group B	1	48	2.08					Dose Titration

Table C52. KQ2: Hypertension

Study ID	Treatment n	Treatment N	Percentage	Control n	Control N	Percentage	Definition of Hypertension	Comments
KQ2 Comparison I. Different Weight-Based Doses								
Kunikane 2001 Group A	3	22	13.64	4	17	23.53	Grade 1-4 reported not further specified	
Kunikane 2001 Group B	2	21	9.52				Grade 1-4 reported not further specified	
Ten Bokkel 1998 Group A	1	45	2.22	1	28	3.58	SBP > 180 mmHg with change < 30 mmHg or SBP < 80 mmHg with change of 15 mmHg or DBP: > 100 mmHg with change > 15mmHG	
Ten Bokkel 1998 Group B	3	42	7.14					
KQ2 Comparison II. Different Fixed Doses								
Glimelius 1998	0	41	0	0	43		NR	
Johansson 2001	0	90	0	0	90	0	NR	
KQ2 Comparison III. Weight-Based versus Fixed-Dose Regimens								
Granetto 2003	4	268	1.5	3	264	1.1	No	Only AE related to study drug reported.
KQ2 Comparison VI. Titrated versus Constant Dosing								
Österborg 1996 Group A	4	47	8.51	1	49	2.04		
Österborg 1996 Group B	5	48	10.42					

Appendix C. Evidence Tables

Table C53. KQ3: Study Characteristics, Part I

study author	participants randomized	Drug	Inter-vention (Early)	Control Late	weight based or fixed	Maximum duration of EPO medication (weeks)	dose adjustment	iron	transfusion trigger (when transfusion assessed)	publication	primary and secondary outcomes of the study
Rearden 2004	204 E: 102 L: 102	Darbepoetin alfa	300 µg Q3W	Observation until Hb≤ 10 g/dl then start treatment 300µg Q3W [38 patients, 37.3%]	Fixed	12 (darbepoetin treatment period); chemotherapy and follow-up continued for 22 weeks	Increase to 500µg /Dose-. for Early: if Hb <10g/dl; for Late: if Hb <9 g/dl or if after 2 consecutives doses of DA Hb <10 g/dl	NR	NR	Abstract + slides	proportions with: Hb drop below 10 g/dl by week 12; Hb drop during therapy; RBC transfused during therapy; also, mean Hb over time; mean change in FACT-Fatigue subscale score; proportion maintaining Hb 11.0 to 13.0 (target)
Straus 2003	269 E: 135 L: 134	Epoetin alfa	40000 IU QW	Observation until Hb≤9 g/dl after 2nd chemotherapy cycle, then start treatment: 40,000 IU QW [29 pt (19.4%)]	Fixed	16	Increased to 60000 in either group if after 4w of Epo treatment Hb I≤1g/dl	NR	NR	Abstract + poster copy	Hb response; RBC transfusions, QoL; Safety Health Care utilization Work / Productivity
Crawford 2003	216 E: 109 L: 107	Epoetin alfa	40000 IU QW	Observation until Hb≤ 10 g/dl, then start treatment at 40,000 IU QW (44% of controls had Hb<10 g/dL and received late epoetin)	Fixed	16	Increased to 60,000 IU QW if ≥2 g/dL Hb decrease; dose withheld if Hb >15 g/dL twice consecutively; re-start with dose decreased by 20,000 IU weekly when Hb ≤13 g/dL	as needed (ferritin <100 ng/mL or Tsat<20%)	NR	Abstract + slides (presented as poster)	Hb changes over time; proportion transfused; RBC units/patient; QoL changes with Fact-An, LASA, BFI; tumor size; survival; adverse events; lab tests; blood pressure

Appendix C. Evidence Tables

Table C54. KQ3: Study Characteristics, Part II

study author	n randomized	cancer details	cancer category	therapy	Hb eligibility criteria [g/dl]	Hb baseline Early [mean g/dl (SD)]	Hb baseline Late arm [mean g/dl (SD)]	Hb cate-gory	Age Early arm [mean (SD)] if not stated otherwise	Age Late arm [mean (SD)] if not stated otherwise	age category (children adults elders (>65)
Rearden 2004	204	Breast; Lung; GiT; Genitourinary; Lymphoid; Gyne; Other	Mixed	chemotherapy	≥10,5 and ≤12,0	11,1 (SD 0,7)	11,2 (SD 0,6)	12	63,2 (SD 10,9)	63,7 (SD 12,2)	Adults
Straus 2003	269	NHL; MM ; Hodgkin; CL	Hematological	chemotherapy with cycles week (1;2;3;4)	Hb > 10 g/dl and Hb ≤12,0 g/dl	11,1(SE 0,7)	11,2 (SE 0,7)	12	59,0 (SD14,0) n=126	60,5 (SD14,9) n = 122	Adults
Crawford 2003	216	Lung cancer (non-small cell)	Solid	chemotherapy with platinum, 78-80% of each arm	Hb ≥11 g/dL and <15 g/dL	13,1 (SD 1,0)	13,0 (SD 1,2)	>12	62,3 (SD 11,0)	62,7 (SD 10,6)	adults

Table C55. KQ3: Study Quality

study author	random	allocation	blinding	placebo	ITT or 10%	similar	high or low quality
Rearden 2004	unclear	unclear	no	no placebo	ITT	yes	low
Straus 2003	unclear	unclear	no	no placebo	ITT	yes	low
Crawford 2003	unclear	unclear	no	no placebo	ITT	yes	Low

Appendix C. Evidence Tables

Table C56. KQ3. Hematologic Response

study author	Hb response definition	Early (n)	Early (N)	Percentage (%)	Late (n)	Late (N)	Percentage (%)	Comments
Rearden 2004	Hb Increase ≥ 2 g/dl	19	94	20,2	16	86	18,6	Data presented by Charu-2004

Table C57. KQ3: Study Not Included for Hematologic Response

study author	Hb response definition	Early	Late	Comments
Straus 2003	Hb increase ≥ 2 g/dl OR Hb increase Hb ≥ 12 g/dl	70,4% (95 Pt)	25,4% (34 Pt)	P < 0,001 (ITT)
Crawford 2003	Proportion maintaining Hb ≥10 g/dL and not transfused	82%	56%	P = 0,0001

Table C58. KQ3: Transfusion

Study ID	time of measurement	Intervention (n)	Intervention (N)	Percentage (%)	Control (n)	Control(N)	Percentage (%)	Comments
Rearden 2004	12 weeks	14	99	14% (CI 7;20)	22	102	22% (CI 13;30)	
Rearden 2004	22 weeks	17	99	17,2	27	102	26,5	P=0,11
Straus 2003	16 weeks	24	135	17,8	35	134	26,1	P=0,11
Crawford 2003	16 weeks	13	106	12,3	22	105	21,0	P=0,089

Table C59. KQ3: Thrombotic Events

Study ID	Intervention n	Intervention N	Percentage (%)	Control n	Control N	Percentage (%)	Definition of TE	Comments
Rearden 2004	99	2	2	102	0	0	1 atrial fibrillation 1 deep venous thrombosis	The other adverse events possibility related to study drug 9 / 5 not specified. described
Straus 2003	135	15	11.1	134	4	3	Thrombovascular events	In Early 2 TVE´s (moderate thrombosis and severe deep thromophlebitis) were assed related to epo, in Late no.
Crawford	NR		NR	NR		NR		

Appendix C. Evidence Tables

Table C60. KQ3: QoL data from Straus et al. 2003

Straus 2003	Baseline Immediate	Change Immediate	Baseline Delayed:	Change: Delayed	p-value
FACT-G					
- FACT –G Physical well being	20.9 (n=117)	1.0 (n=118)	20.9 (n=112)	-0.33 (n=112)	0.007
- FACT –G Functional well being	17.6 (n=118)	0.43 (n=119)	18.3 (n=114)	- 1.03 (n=113)	0. 024
FACT – anemia subscale					
- FACT – fatigue subscale	34.0 (n=118)	1.45 (n=119)	34.3 (n=112)	- 1.68 (n=112)	0.005
- Total of FACT anemia subscale	55.0 (n=118)	1.92 (n=118)	55.2 (n=112)	- 1.71 (n=112)	0.008

Table C61. KQ3: QoL data from Rearden et al. 2004

Rearden 2004	Baseline Immediate	Change (week 13) Immediate	Change (week 22) Immediate	Baseline Delayed:	Change (week 13) Delayed	Change (week 22) Delayed	comments
- FACT – fatigue subscale		n=86	n=72		n=72	n=52	
	31.6 (SD11.7)	1.5 (CI 4.0;-0.9)	1.5 (CI 4.4;-1.4)	27.7 (SD 12.8)	-0.8 (CI 2.1;-3.6)	1.8 (CI 5.7;-1.9)	Fact F baseline data from Charu et al. 2004

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Miller 1992	Phase I/II	I	Determine association of pretreatment variables with HR		Full text	21	12/21 (57%)	NR/NA	Hb > 10 g/dL after 3-4 weeks independent of transfusion	Different response criterion; unclear if all possible predictive factors that had been tested are reported
Case 1993	RCT	I	Use a linear model approach to determine the effect of various baseline parameters on response efficacy	12	Full text	157 (81 rec'd Epo)	46/79 (58%)	NR	Hct increase ≥ 6% from baseline independent of transfusion	Patients probably included in Henry 1995
Cascinu 1994	RCT	I	Determine the association of pretreatment erythropoietin levels with response to epo treatment	9	Full text	100 (50 rec'd Epo)	29/50 (58%) after 3 wks 37/50 (74%) after 6 wks 41/50 (82%) after 9 wks	NR	Hb increase to > 10 g/dL after 3, 6, and 9 weeks	Different response criterion
Ludwig 1994	Prospec-tive cohort study	I	Investigate the power of hematological and humoral factors to predict response to epo	≥12	Full text	80	38/80 (48%)	9/38 (24%) of responders	Hb increase ≥ 2 g/dL within 12 weeks and no transfusion within weeks 3-12	Unclear if patients received chemo-radiotherapy

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I (cont'd)

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Cazzola 1995	RCT	I	Identify predictors of response to epo	8	Full text	146 (117 rec'd Epo)	After 8 weeks: 5,000 IU: 61% 10,000 IU: 62%	NR	Hb increase ≥ 2 g/dL between baseline and two time points independent of transfusion in the previous 6 wks (unclear if different definition used for predictive factors study: "cumulative response rates after 8 weeks of treatment")	Two additional dose-levels were investigated (1000 IU and 2000 IU) but excluded for predictive factors study
Garton 1995	RCT	I	Determine differences between responders and non-responders (not explicitly stated)	6	Full text	10	9/20 (45%) including all pts 6/10 (60%) including only patients receiving Epo in the first part of the study	7/9 responders received 3 x 300 IU/kg/wk	Hct ≥ 38% after 12 weeks of epo	Different response definition; unclear what kind of chemo- or radiotherapy patients received
Henry 1995	RCT	I	Re-analysis of data to predict responsiveness to Epo	12	Full text (letter)	NR	77/143 (54%; only patients receiving chemotherapy)	NR	Hct increase ≥ 6% after 12 weeks from baseline independent of transfusion	Only results for patients receiving chemotherapy reported here
Ludwig 1995	Prospec-tive cohort study	I	Determine the association of baseline erythropoietin levels and changes over time with HR	12	Full text	102	35/68 (51%; only patients receiving chemotherapy)	NR	Hb increase ≥ 2 g/dL independent of transfusion	
Osterborg 1996	RCT	I	Identify prognostic factors for HR	24	Full text	121 (77 rec'd Epo)	60%	NR	Hb increase ≥ 2 g/dL (mean over 4 wks) independent of transfusion (8 wk period)	

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I (cont'd)

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Kasper 1997	Prospec-tive cohort study	I	Compare baseline parameters of responders and non-responders (not explicitly stated)	≥12	Full text	60	23/48 (48%)	59/60 (98%) not reported separately for predictive factors analysis	Hb increase > 2g/dL from baseline independent of transfusion	
Glaspy 1997	Prospec-tive cohort study	I	Determine the association of baseline erythropoietin level with change in hemoglobin level during epo therapy	Unclear (1047 patients received 4 months)	Full text	2342 (2030 evaluable)	53%	NR	Different definitions used for different analyses; not all definitions reported	Recommended that epo not be started unless erythropoietin level at baseline < 200 IU/L; collection of baseline data (e.g. erythropoietin level) optional; different response definition
Musto 1997	Prospec-tive cohort study	I	Evaluate the role of interleukin-1, interleukin-6, tumor necrosis factor and other non-invasive factors in erythropoiesis	8	Full text	40 (40 rec'd Epo)	13/37 (35%)	NR/NA	Complete interruption of transfusions and stable Hb > 8 g/dL	Different response definition
Demetri 1998	Prospec-tive cohort study	I	Determine the association of baseline erythropoietin levels and response (not explicitly stated)	16	Full text	2370 (2289 evaluable)	1406/2289 (61%)	NR	Hb increase ≥ 2 g/dL or Hb ≥ 12 g/dL	Different response criterion; unclear if absence of transfusion required; response definition probably not used for predictive factors study; statistical methods inadequately described

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I (cont'd)

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Fjornes 1998	Prospec-tive cohort study	I	Develop prediction criteria for efficacy of epo therapy	12	Full text	22 (22 rec'd Epo)	10/22 (45%)	NR	No transfusions required, no decrease in Hb level, or improved performance status with decreased clinical symptoms of anemia (3 criteria "very good response", 2 criteria "good response", 1 criterion "moderate response")	Different response criterion
Glimelius 1998	RCT	I	Determine the association of baseline erythropoietin levels and response (not explicitly stated)	18	Full text	100	2000 IU: 30% 10000 IU: 73%	NA	Hb increase ≥ 1.0 g/dL independent of RBCT	Different response definition
Oberhoff 1998	RCT	I	Identify subgroups of patients that exhibit the greatest epo benefit	12	Full text	189 (101 in Epo-arm)	38%	NR/NA	Hb increase ≥ 2 g/dL in a 4 wk interval and maintained independent of transfusion in that interval or the previous 4 wks	Transferrin saturation mentioned as possible predictive factor in methods section but not reported in results
Gonzalez 1999	Prospec-tive cohort study	I		NR	Abstract		40/79 (51%) type I 23/79 (29%) type II	NR	Hb increase ≥ 1 g/dL after 4 weeks (type I); Hb increase ≥ 1 g/dL after 8 weeks (on double epo dose) (type II)	Different response criterion; unclear if absence of transfusion required
González-Barón 2002	Prospec-tive cohort study	I	Identify factors that might predict HR to epo	1 month after end of chemo-therapy (median 2.9 cycles)	Full text	117	63%	NR	Hb increase ≥ 2 g/dL during the treatment phase	Unclear if absence of transfusion required

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I (cont'd)

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Hedenus 2002	RCT	I	Use logistic regression model to assess the treatment effect of darbepoetin alfa and other parameters	12	Full text	66 (55 rec'd Epo)	1.0 µg/kg: 45%; 2.25 µg/kg: 55%; 4.5 µg/kg: 62%	Epo stopped temporarily in 3 patients; no details reported	Hb increase ≥ 2 g/dL independent of transfusion in the previous 4 wks	
Boogaerts 2003	RCT	I	Determine the association between endogenous erythropoietin level and HR to epo	12	Full text	262 (133 rec'd Epo)	63/133 (47%)	NR	Hb increase ≥ 2 g/dL during the treatment phase without transfusion after the initial 4 treatment wks	Statistical methods inadequately described
Cazzola 2003	RCT	I	Identify predictors of response to epo	16	Full text	241 (241 rec'd Epo)	tiw: 75% qw: 72%	NR	Hb increase ≥ 2 g/dL from baseline independent of transfusion in the previous 6 wks	Additional inclusion criterion: serum epo level ≤ 100 IU/L; unclear if all possible factors analyzed were reported
Chang 2004	RCT	I	Exploratory analysis to determine which baseline parameters were significant predictors of HR	16 or 4 wks after end of chemotx (max 28 weeks)	Full text	354	52%	NR	Calculated average Hb from wks 4 to 12 ≥ 12 g/dL	Statistical methods inadequately described; unclear if absence of transfusion required; different response criterion
Katodritou 2004	Prospec-tive cohort study	I	Evaluate both traditional and novel predictive factors for predicting response to Epo treatment	≥6 (responders continued as needed; non-responders plus iron for additional 4 weeks)	Abstract	NA	20/32 (63%)	NR/NA	Hb increase ≥ 2 g/dL after 6 wks; Patients with iron plus epo: Hb increase ≥ 1 g/dL after 4 weeks	Unclear if absence of transfusion required; 20/32 (63%) responders, 12/32 (38%) non-responders (8/9 iron+Epo responded)

Appendix C. Evidence Tables

Table C62. KQ4: Study Characteristics, Part I (cont'd)

Study Author	Trial Design	Study Type	Objective	EPO Tx Length (wks)	Source	No. of Patients in Study	Hb Response N Resp/ N Eval (%)	No. Pts. With Dose Change	Definition of Hb Response	Comment
Witzig 2004	RCT	II	Test a modified version of a specific algorithm (Ludwig 1994) to predict HR	16	Full text	344 (174 in Epo-arm)	73%	Dose escalation: 42.8%	Hb increase ≥ 2 g/dL	Different response criterion (HR not independent of transfusion); statistical methods not described
Littlewood 2003	4 RCT	I	Determine the relationship between a large number of pre- and early treatment factors and HR	NR	Full text	604	382/561 (68%)	NR	Hb increase ≥ 2 g/dL or Hct increase ≥ 6%	Unclear if absence of transfusion required; no study analyzed here reported elsewhere in table
McKenzie 2004	3 multi-center clinical trials	I	Evaluate whether patients with early Hb increase had better outcomes compared with late/non-responders	NR	Abstract	Study 1: 2964; study 2: 681; study 3: 2289	NR	NR	Hb increase ≥ 2 g/dL independent of transfusion	Patients probably already included in Glaspy 1997 and Demetri 1998

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Miller 1992	Epoetin beta	5 x 25, 50, 10, or 200 IU/kg/wk	NR	NR	HR, Hb, RBCT, AE	Solid tumors	chemotx (all platinum)	< 11 g/dL while receiving chemo; > 11 g/dL if prior to chemo	10.0 g/dL (9.3)	Mean 51 yrs (SD 6)
Case 1993	Epoetin alfa	3 x 150 IU/kg/wk	Decreasing: if Hct 38-40%; epo dose titrated to maintain Hct	Discretion of treating physician	HR, RBCT, HRQOL, AE	Malignancy (excluding primary myeloid malignancies and acute leukemias)	chemotx	≤ 10.5 g/dL	Hct 28.5% (Hb not reported)	64 yrs (27-92)
Cascinu 1994	Epoetin alfa	3 x 100 IU/kg/wk	Decreasing: if Hb > 12 g/dL; epo stopped until Hb <10 g/dL	Hb < 8 g/dL or clinical symptoms	HR, Hb, RBCT, AE	Stomach, ovarian, melanoma, head neck, lung, breast	chemotx (platinum all); some radiotherapy	≤ 9 g/dL	8.6 g/dL (0.6)	58 yrs (44-72)
Ludwig 1994	Epoetin alfa	3 x 150 IU/kg/wk	Increasing/ decreasing: if Hb increase < 2 g/dL after 6 wks epo 3 x 300 IU/kg/wk; epo titrated to maintain Hb in normal range	NR	Not applicable	Multiple myeloma, breast, other hematologic malignancies and solid tumors	Unclear	< 11 g/dL	Median 9.5 g/dL (range 5.3-10.9)	62 yrs (32-82)
Cazzola 1995	Epoetin beta	7 x 5,000 or 10000 IU/wk (see comment)	Decreasing: if Hb increase > 2 g/dL or Hb > 12.5 g/dL epo 3 x per week; epo stopped if Hb > 13 g/dL (MM) or > 15 g/dL (NHL)	Discretion of treating physician	HR, Hb, RBCT, AE	Multiple myeloma, non-Hodgkin lymphoma (excluding high-grade NHL)	chemotx (116/146 (79%) of patients)	≤ 11 g/dL (independent of transfusion)	5000 IU: 9.4 g/dL (1.2); 10000 IU: 9.4 g/dL (1.0)	5000 IU: 68 yrs (42-85); 10000 IU: 63 yrs (28-80)
Garton 1995	Epoetin alfa	3 x 150 IU/kg/wk	Increasing: if Hct < 38% after 6 wks Epo 3 x 300 IU/kg/wk for6 more wks	NR	HR	Multiple myeloma	chemotx	Hct ≤ 30% (unrelated to recent bleeding)	Hct 29% (Hb not reported)	NR
Henry 1995	NR	3 x 150 IU/kg/wk	NR	NR	HR, RBCT, HRQOL, AE	Hematologic malignancies, prostate, breast, GI-tract, lung, other solid tumors	chemotx	≤ 10.5 g/dL or Hct ≤ 32% (from Abeles 1993)	Hct 29.1 % (including pts not receiving chemotx; from Abeles 1993)	NR

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Ludwig 1995	NR	3 x 150 IU/kg/wk	Increasing/decreasing: if Hb increase ≤ 2 g/dL epo 300 IU/kg; if Hb > 12 g/dL epo dose reduced at discretion of treating physician	If clinical symptoms required immediate medical attention	HR, RBCT, performance status, AE	Breast, multiple myeloma, other solid tumors, other hematological malignancies (including CLL)	chemotx (68/94 (72%) of patients; 15/68 (22%) platinum)	< 11 g/dL	9.2 g/dL (1.1; only pts receiving chemotx)	57 yrs (33-86; only patients receiving chemotx)
Osterborg 1996	Epoetin beta	7 x 10,000 IU/wk or titration (7 x 2,000 IU/wk week 1-8; 7 x 5,000 IU/wk week 9-12; 7 x 10,000 IU/wk week 13-24)	Decreasing: if Hb 11-13 g/dL (no RBCT) epo 5 or 3 times per week; epo stopped if Hb > 13 g/dL (women) or > 14 g/dL (men) until Hb ≤ 10 g/dL (reduced frequency)	Hb < 10 g/dL	HR, RBCT, AE	Multiple myeloma, low-grade NHL	chemotx (69/77 (90%) of patients receiving Epo)	≤ 10 g/dL	Fixed dose: median 8.0 g/dL (range 6.2-10.1); titration: median 8.0 g/dL (range 5.2-9.8)	Fixed dose: 66 yrs (43-84); titration: 64 yrs (36-83)
Kasper 1997	NR	7 x 2,000 IU/wk	Increasing/decreasing: if Hb increase ≤ 2 g/dL after 4 wks epo 7 x 5,000 IU/wk; if Hb increase ≤ 2 g/dL after 8 wks Epo 7 x 10,000 IU/wk; if Hb ≥ 14 g/dL epo 5 x /wk or 3 x /wk; epo stopped if no HR after 12 wks, stable Hb, or Hb >16 g/dL	NR	HR	Hematologic malignancies (including CLL and MDS), solid tumors	chemotx (85% of patients)	< 10 g/dL	9.2 g/dL (0.1)	53 yrs (18-71)

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Glaspy 1997	Epoetin alfa	3 x 150 IU/kg/wk	Increasing/decreasing: if response not satisfactory to treating physician epo 3 x 300 IU/kg/wk; if Hct increase > 4% during 2-wk period epo reduced 25%; epo stopped if Hct > 40% until Hct ≤ 38% (epo reduced 25%)	NR	HR, HRQOL, RBCT	Hematologic malignancies (excluding myeloid malignancies), lung, breast, gynecologic malignancies, other solid tumors	chemotx (40% platinum-based)	Anemia (no further details reported)	9.2 g/dL (1.3)	Mean 62.2 yrs (SD 13.3)
Musto 1997	Epoetin alfa	3 x 10,000 IU/wk	NR	NR	HR	Multiple myeloma	chemotx	≤ 8 g/dL (transfusion required)	Median 7.1 g/dL (range 3.5-8)	64.2 yrs (42-78)
Demetri 1998	Epoetin alfa	3 x 10,000 IU/wk	Increasing/decreasing: if Hb increase after 4 wks <1 g/dL epo 3 x 20,000 IU/wk; if Hb increase > 1 g/dL within 2-wk period epo dose reduced; epo stopped if Hb > 13 g/dL until ≤ 12 g/dL (epo dose reduced by 25% and titrated to maintain Hb level) or if Hb increase after 8 wks < 1 g/dL	Discretion of treating physician	HR, Harold, RBCT	Lung, hematologic malignancies (excluding myeloid malignancies), breast, gynecologic malignancies, other solid tumors	chemotx (21% platinum)	≤ 11 g/dL	9.3 g/dL (1.0)	Mean 63 yrs (SD 13)

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Fjornes 1998	Epoetin alfa	3 x 10000 IU/wk	Increasing/decreasing: if Hb after 4 weeks decreased from baseline, stable/decreased performance status, or stable/increased clinical symptoms of anemia Epo 3 x 20,000 IU/wk; Epo stopped if transfusion required for decreasing Hb levels and worsened performance status	Hb < 8.5 g/dL and clinical signs of anemic hypoxia	HR, Hb, RBCT	Lung, sarcoma, breast, neuroectodermal	chemotx (platinum all)	< 11 g/dL	Median 8.1 g/dL (range 5.9-10.9)	71 yrs (48-94)
Glimelius 1998	Epoetin beta	3 x 2,000 or 10,000 IU/kg/wk	Not allowed; epo stopped if Hb > 14.5 g/dL	If Hb < 8.5 g/dL at discretion of physician	HR, RBCT, HRQoL, AE	Colorectal, other GI-tract malignancies	chemotx (16/100 (16%) patients received no chemotx)	Men: ≤ 13 g/dL (chemo) and ≤ 11.5 g/dL (no chemo); women: ≤ 11.5 g/dL (chemo) and ≤ 10.5 g/dL (no chemo)	2,000 IU (chemo): 10.8 g/dL (1.0); 2,000 IU (no chemo): 9.7 g/dL (0.9); 10,000 IU (chemo): 10.9 g/dL (1.0); 10,000 IU (no chemo): 9.9 g/dL (0.7)	2000 IU (chemo): Mean 61 yrs (range 34-79); 2000 IU (no chemo): Mean 63 yrs (range 46-80); 10000 IU (chemo): Mean 61 yrs (range 31-78); 10000 IU (no chemo): Mean 64 yrs (range 53-75)
Oberhoff 1998	Epoetin beta	7 x 5,000 IU/wk	NR	NR	RBCT, HR, AE	Gynecological malignancies, breast, lung, urinary tract cancer, other solid tumors	chemotx (> 50% platinum)	≤ 11 g/dL	Median 9.6 g/dL	53 yrs (20-77)

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Gonzalez 1999	Epoetin alfa	3 x 150 IU/kg/wk	Increasing: if Hb increase after 4 wks < 1 g/dL epo 3 x 300 IU/kg/wk	NR	Not applicable (predictive factors = study objective	Solid tumors	chemotx (platinum all)	≤ 11 g/dL	NR	NR
González-Barón 2002	Epoetin alfa	3 x 150 IU/kg/wk	No dose adjustment in first 4 wks according to HR (no details reported)	NR	Not applicable	Lung, ovarian, other	chemotx (platinum all)	≤ 10.5 g/dL	NR	Mean 54.8 yrs
Hedenus 2002	Darb-epoetin alfa	1 x 1.0, 2.25, or 4.5 µg/kg/wk	Decreasing: if Hb increase during 28d period (plus absence of RBCT) ≥ 2 g/dL epo reduced by 50%; epo stopped if Hb > 15 g/dL (men) or 14 g/dL (women) until Hb ≤ 13 g/dL (epo dose reduced by 50%)	Hb ≤ 8 g/dL	HR, Hb, RBCT, AE	Multiple myeloma, lymphoma (including CLL but excluding high-grade NHL)	chemotx	≤ 11 g/dL	1.0 µg/kg: 9.7 g/dL (0.8); 2.25 µg/kg: 9.4 g/dL (1.3); 4.5 µg/kg: 9.7 (0.9)	1.0 µg/kg: 64 yrs (26-80); 2.25 µg/kg: 69 yrs (20-84); 4.5 µg/kg: 70 yrs (52-84)
Boogaerts 2003	Epoetin beta	3 x 150 IU/kg/wk	Increasing/decreasing: if Hb increase within 3-4 wks < 0.5 g/dL or < 1 g/dL within 6-8 wks epo 3 x 300 IU/kg/wk; if Hb increase within 4 wks > 2 g/dL epo dose reduced 50%; epo stopped if Hb > 14 g/dL until Hb < 12 g/dL (epo dose reduced 50%)	Hb < 8.5 g/dL	HR, Hb, RBCT, QoL	Multiple myeloma, lymphoma (including CLL), ovarian, sarcoma, colorectal, lung, other solid tumors	chemotx (platinum some; assumed)	≤ 11 g/dL	Median 9.0 g/dL (range 5-13)	62 yrs (24-85)

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Cazzola 2003	Epoetin beta	3 x 10,000 IU/wk (tiw) or 1 x 30,000 IU/wk (qw)	Increasing/decreasing: if no response after 4 wks epo dose doubled; if Hb increase ≥ 2 g/dL epo dose reduced by 50%; epo stopped if Hb > 14 g/dL until Hb < 13 g/dL (epo dose reduced by 50%)	Hb < 8.5 g/dL unless clinically indicated	Hb AUC5-16, HR, Hb, RBCT, several other efficacy parameters	Multiple myeloma, lymphoma (including CLL)	chemotx (32/237 (14%) of patients received no chemotx)	9-11 g/dL	tiw: 10.1 (1.0); qw: 10.2 (1.0)	tiw: 65 yrs (33-90); qw: 67 yrs (38-82)
Chang 2004	Epoetin alfa	1 x 40,000 IU/wk	Increasing/decreasing: if Hb after 4 or 6 wks decreased > 2 g/dL epo 1 x 60,000 IU/wk; if Hb increase > 2 g/dL/month epo reduced 25% (to maintain Hb increase at < 2 g/dL/mo); epo stopped if Hb > 14 g/dL until Hb ≤ 12 g/dL (epo dose reduced 25%)	Discretion of treating physician (not recommended unless Hb < 8 g/dL)	HRQoL, AE	Breast	chemotx	≤ 12 g/dL	11.2 g/dL (0.9)	Mean 50.4 yrs (SD 11.1)
Katodritou 2004	NR	30,000 IU/wk	NR	NR	Not applicable (predictive factors = study objective)	Multiple myeloma, lymphoma	NR	NR	NR	NR
Witzig 2004	Epoetin alfa	1 x 40,000 IU/wk	Increasing: if Hb increase < 1 g/dL after 4 wks epo 1 x 60,000 IU/wk; epo stopped if Hb > 15 g/dL for two wks until Hb < 13 g/dL (epo dose reduced 25%)	At discretion of physician	HRQoL, RBCT, Hb	Lung, breast cancer, other	chemotx (some platinum); some radiotherapy	≤11.5 g/dL (men); ≤10.5 g/dL (women)	9.5 g/dL (range 6.0-11.4)	63.6 (11.89)

Appendix C. Evidence Tables

Table C63. KQ4: Study Characteristics, Part II (cont'd)

Study Author	Drug	Dose per week	Dose Change	Transfusion trigger	Out-comes Reported	Malignancy type	Cancer Tx	Hb required at enrollment	Baseline Hb g/dL (SD)	Age (Med. Range)
Littlewood 2003	NR	3 x 150 IU/kg/wk	Increasing (3 studies): if Hb increase < 1 g/dL after 4 wks epo 3 x 300 IU/kg/wk; Decreasing (1 study):epo titrated to achieve Hct 38-40%	NR	NR	Breast cancer (23%), multiple myeloma (20%), lymphoma (16%), other	NR (probably > 50% chemotx)	NR	NR	Median 62 yrs (range 18-92)
McKenzie 2004	NR	Study 1 and 2: 40,000 IU/wk; study 3: 3 x 10,000 IU/wk	Study 1 and 2: escalation to 60,000 IU/wk possible; study 3: escalation to 3 x 20,000 IU/wk possible	NR	NR	Nonmyeloid malignancies	chemotx; some radiotherapy	≤ 11 g/dL	NR	NR

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Miller 1992	I	No	Yes	Unclear	No	Unclear (probably no patients excluded but no explicit statement)	No	No	Yes	No	No/not applicable (unclear if cut-offs were used)	No	Univariate logistic regression models
Case 1993	I	No	Yes	Yes	No	Partially (2 excluded for analysis)	No	No	Yes	No	Not applicable	No	Multivariate linear regression
Cascinu 1994	I	No	Yes	Unclear	No	Unclear (probably no patients excluded but no explicit statement)	No	No	Yes	No	No	No	Univariate logistic regression

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Ludwig 1994		No	Yes	Unclear	No	Unclear (probably no patients excluded but no explicit statement)	Unclear	Yes (sample was split in a training and verification group; patients were ordered chronologic ally (?) and alternately assigned to one of the two groups)	Yes	No	Yes (various percentiles were tested with stepwise discriminant analysis)	No	Point-biserial correlation to estimate correlation of baseline parameters and HR; stepwise discriminant analysis (selection criterion for variables/cu t-offs: likelihood ratio approach (measured by statistically significant Wilks' lambda)); Cox's maximum likelihood multivariate logistic regression for defining the algorithm

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Cazzola 1995	I	Yes	Yes	Unclear	No	No	Partially (lost to follow-up because of death, AE, or non-response: coded as non-response; other losses to follow-up: censored)	No	Yes	No	Yes (using repeated log-rank tests cut-off values were chosen that divided patients into groups with high or low probability of response (>/= 10 patients in group)	Partially (for algorithm)	Time to response: Kaplan-Meier; univariate methods (repeated log-rank tests for optimal cut-offs); classificatio n and regression tree method; Cox proportional -hazard model (if two or more factors were found)
Garton 1995	I	No	No	Unclear	No	Partially (4 excluded for analysis	No	No	Yes	No	Not applicable	No	Univariate methods (Student's t-test)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Henry 1995	I	No	Yes	Unclear	No	No	No (seems some patients were lost to follow-up for early changes: 2 weeks 132 patients included; 4 weeks 127 patients included)	No	Yes	Partially	Partially	No	Descriptive statistics
Ludwig 1995	I	No	Yes	Yes (baseline erythropoiet in level available)	No	Partially (48 excluded for analysis	No	No	Yes	No	No	No	Not reported (odds ratio and 95%-CI reported in results)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Osterborg 1996	I	No	Yes	No	No	No	No	No	Yes	No	Univariate analysis: not applicable; multivariate analysis: partially (several analysis performed with different cut-offs but unclear how the optimal one was chosen)	No	Univariate and multivariate Cox's regression model
Glaspy 1997	I	No	Partially	No	No	No	No	No	Yes	Yes (literature reference)	Not applicable	No	Simple linear correlation using regression analysis
Kasper 1997	I	No	Partially	No	No	Yes (12 excluded for analysis)	Yes (simple exclusion from analysis)	No	Yes	No	No/not applicable (unclear if cut-offs were used)	Partially	Univariate methods (Student's t-test, Mann-Whitney U-Wilcoxon rank sum test (according to the results only t-test was used)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Musto 1997	I	No	Yes	Yes	No	Yes (3 excluded for analysis)	Partially	No	Yes	Partially	Partially (medians were chosen as cut-offs)	No	Univariate methods (chi-square test)
Demetri 1998	I	No	Unclear	Yes	No	Partially (1317 excluded for analysis of baseline erythropoiet in level)	Yes (simple exclusion from analysis)	No	Yes	No	Not applicable	No	Descriptive statistics (early changes) and regression analysis (baseline erythropoiet in level)
Fjornes 1998	I	No	Yes	Unclear	No	Unclear (probably no patients excluded but no explicit statement)	No	No	Yes	No	Not applicable	No	Univariate methods (Mann-Whitney U-test)
Glimelius 1998	I	No	Unclear	Unclear	No	No	No	No	Yes	Yes (literature reference)	No (apparently various cut-offs were used for Epo O/P ratio and at least one cut-off was used for baseline erythropoiet in level)	No	Univariate methods (Student's t-test and chi-square test)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Oberhoff 1998	I	No	Yes	No	No	No	Unclear	No	Yes	No	No	No	Unclear
Gonzalez 1999	I	No	Yes	No	No	Partially (26 excluded for analysis)	No	No	Yes	No	No/not applicable (unclear if cut-offs were used)	No	Not reported

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
González-Barón 2002	I	No	Yes	Yes (at least 4 weeks on Epo treatment; however patients were also excluded for other reasons: receiving RBCT during first 4 weeks, death caused by malignancy, fewer than 3 chemothera py cycles, no follow-up data for the first 4 weeks)	No (post-hoc 'power-analysis' using 95%-confidenc e intervals reported)	Partially (27 excluded for analysis)	Yes (last observatio n carried forward)	Yes (six samples (using 45 (50% of the whole sample) randomly selected case; however, no results of this validation are reported)	Yes	No	Unclear	Yes	Univariate analysis; point-biserial correlation to estimate correlation of baseline parameters and early changes and HR; stepwise discriminant analysis (selection criterion for variables: likelihood ratio approach (measured by statistically significant Wilks' lambda)); logistic regression models (cut-off values were chosen based on the maximum verisimilitud e method)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Hedenus 2002	I	No	Yes	Yes	No	Partially (unclear if 2 excluded for analysis)	No	No	Yes	No	No	No	Multiple logistic regression
Boogaerts 2003	I	No	Yes	Yes	No	Partially (30 withdrawn during study)	No	No	Yes	Partially	No (paper cited for justification described different cut-off values/used no cut-off values	No	Odds ratios and relative risks (no further details reported, e.g. statistical tests used)
Cazzola 2003	I	No	Yes	Unclear	No	Unclear	Partially (8 patients were excluded from the primary ITT analysis; however, it is unclear which population was used for the predictive factors analysis	No	Yes	No	Unclear	No	Cox proportional -hazard model

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Chang 2004	I	No	Yes	Unclear	No	Unclear	No	No	Yes	No	No/not applicable (unclear if cut-offs were used)	No	Multivariate logistic regression
Katodritou 2004	I	No	Yes	Yes	No	Unclear (probably no patients excluded but no explicit statement)	No	No	Yes	Partially	No/not applicable (unclear if cut-offs were used)	Yes	Univariate and multivariate methods (no further details reported); ROC curve to determine optimal cut-offs for factors significant in multivariate analysis
Witzig 2004	II	No	Yes	No	No	No	No	No	Yes	Partially	Partially	Partially	Descriptive and univariate (tests used not reported)

Appendix C. Evidence Tables

Table C64. KQ4: Study Quality, Part I (cont'd)

study author	Type of predic-tive factors study	Refutable hypo-theses reported	Objective prospec-tively defined	Inclusion criteria defined for predictive factors study	Sample size calcula-tion (method)	Number and character-istics of excluded patients reported	Missing data handling reported, including losses to follow-up reported	Internal validation (method)	F/U at least four weeks	Selection process of possible predictive factors explained and adequate	Cut-off values for contin-uous variables explained and adequate	Perform-ance measures reported (Sens., Spec., +LR, -LR)	Method of statistical analysis
Littlewood 2003	I	No	Yes	Partially (data suitable for evaluation available)	No	No	No	No	Yes	Yes (factors addressed in previous studies)	Unclear (some cut-offs chosen based on previous studies, some cut-offs chosen based on multiple testing but no selection criteria reported)	Yes	Stepwise logistic regression analysis for selecting significant variables; univariate methods (chi-square test)
McKenzie 2004	I	No	Yes	No	No	No	No	No	Yes	No	Not applicable	No	Univariate methods (no details reported)

Appendix C. Evidence Tables

Table C65. KQ4: Study Quality, Part II

			Multivariable analysis				
study author	**Prognostic variables fully defined**	**CIs report-ed**	**Statistical package used**	**Coding of variables reported**	**Problem with overfitting**	**Conformity of linearity for ranked variables reported**	**Tests of interaction performed**
Miller 1992	No	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Case 1993	Yes	No	Not reported	Not applicable	Probable	Not applicable	Not reported
Cascinu 1994	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Ludwig 1994	Yes	Yes (odds ratios)	No	Not applicable	Probably	Not applicable	Not reported
Cazzola 1995	Yes	No	SAS	Not applicable	Probable	Not applicable	Not reported
Garton 1995	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Henry 1995	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Ludwig 1995	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Osterborg 1996	Yes	No	No	Univariate analysis: yes; multivariate analysis: not applicable	Unlikely	Not applicable	Not reported
Glaspy 1997	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Kasper 1997	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Musto 1997	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Demetri 1998	Yes	No	Yes (SAS)	Unclear	Unclear	Unclear	Unclear
Fjornes 1998	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Glimelius 1998	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Oberhoff 1998	Yes	No	Not applicable/ reported	Not applicable/ reported	Not applicable/ reported	Not applicable/ reported	Not applicable/ reported
Gonzalez 1999	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Appendix C. Evidence Tables

Table C65. KQ4: Study Quality, Part II (cont'd)

			Multivariable analysis				
study author	**Prognostic variables fully defined**	**CIs report-ed**	**Statistical package used**	**Coding of variables reported**	**Problem with overfitting**	**Conformity of linearity for ranked variables reported**	**Tests of interaction performed**
González-Barón 2002	Yes	No	No	Not applicable	Probable	Not applicable	Not reported
Hedenus 2002	Yes	No	Not reported	Yes	Probable	Not applicable	Not reported
Boogaerts 2003	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Cazzola 2003	Yes	Yes	Not reported	Not applicable	Unlikely	Not applicable	Not reported
Chang 2004	Yes	No	Not reported	Not applicable	Probable	Not applicable	Not reported
Katodritou 2004	Yes	No	Not reported	Not reported	Not reported	Not reported	Not reported
Witzig 2004	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Littlewood 2003	Yes	No	Yes (SAS)	Not applicable	Probable	Not applicable	Not reported
McKenzie 2004	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Appendix C. Evidence Tables

Table C66. KQ4: Serum O/P Ratio

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
Miller 1992	No	Not applicable	Not applicable	Ability to respond independent of baseline erythropoietin level (p = 0.71)	Not reported/assessed	Different response criterion
Case 1993	No	Not applicable	Not applicable	Response to Epo independent of baseline erythropoietin level	Not reported/assessed	Epo level one of various covariates in a multivariate linear regression model; no further details reported (e.g. p-value)
Cascinu 1994	No	Not applicable	Not applicable	Response to Epo independent of baseline erythropoietin level (p = 0.27)	Not reported/assessed	No further details reported
Ludwig 1994	Unclear	Not reported/applicable	Not reported/applicable	Baseline erythropoietin level correlated significantly with responders (r = -0.23; p < 0.05) and discriminated significantly between responders and non-responders (R^2 = 0.074; p < 0.05)	Not reported/assessed	
Cazzola 1995	Yes (baseline erythropoietin level 50 IU/l or 70 IU/l; baseline erythropoietin O/P ratio 0.8 or 0.9)	Baseline erythropoietin level > 50 IU/l: 25%; baseline erythropoietin level > 70 IU/l: 18%; O/P ratio > 0.8: 31%; O/P ratio > 0.9: 27%	Baseline erythropoietin level ≤ 50 IU/l: 78%; baseline erythropoietin level ≤ 70 IU/l: 73%; O/P ratio ≤ 0.8: 75%; O/P ratio ≤ 0.9: 70%	Not reported	Not reported	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; > 50 IU/l versus ≤ 50 IU/l: p = 0.0014 (CART, adjusted); > 70 IU/l versus ≤ 70 IU/l: p = 0.0089 (CART, adjusted); > 0.8 versus ≤ 0.8: p = 0.0050 (CART, adjusted); > 0.9 versus ≤ 0.9: p = 0.0390 (CART, adjusted); according to Cox model epo level independent significant factor (≤ 50 IU/l or O/P ratio ≤ 0.8 more likely to respond); response definition used unclear

Appendix C. Evidence Tables

Table C66. KQ4: Serum O/P Ratio (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
Garton 1995	No	Not applicable (11/20 responder)	Not applicable	Mean erythropoietin level did not differ between responders and non-responders (p = 0.23)	Not reported/assessed	Very few patients
Henry 1995	Yes (baseline erythropoietin level 50 IU/l)	Baseline erythropoietin level ≥ 100 IU/l: 29/64 (45%)	Baseline erythropoietin level < 100 IU/l: 48/79 (61%)	Specificity: 35/66 (53%); sensitivity 48/77 (62%); +LR: 1.3; -LR: 0.7 [test positive: Epo < 100 IU/l; target: response]	Not reported/assessed	Performance measures ("Result") calculated by S.T.; only patients receiving chemotherapy reported here
Ludwig 1995	Yes (baseline erythropoietin level 100 IU/l)	Not reported	Not reported	Responders had more often baseline erythropoietin levels < 100 IU/l compared to non-responders (odds ratio: 0.69; 95%-CI: 0.26-1.80)	Not reported/assessed	
Osterborg 1996	Univariate analysis: no; multivariate analysis: yes (baseline erythropoietin O/P ratio 0.9)	O/P ratio ≥ 0.9: 10% (titration); 41% (fixed dose)	O/P ratio < 0.9: 79% (titration); 60% (fixed dose)	In a further analysis optimal cut-offs for response and non-response were explored (Kaplan Meier estimates): baseline erythropoietin level < 50 IU/l: 76% responded; baseline erythropoietin level ≥ 400 IU/l: 9% responded	Univariate analysis: hazard ratio 0.84 (p-value < 0.01); multivariate analysis: O/P ratio only significant factor; in a further analysis optimal cut-offs for response and non-response were explored (Kaplan-Meier estimates): O/P ratio < 0.6: 89% responded; O/P ratio ≥ 1.2: 10% responded	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; unclear what criteria were applied to find optimal cut-offs in the additional exploratory analysis ("further analysis" in "Results")
Glaspy 1997	No	Not applicable	Not applicable	No correlation between response and baseline erythropoietin level (p = 0.294; r = 0.020)	Not reported/assessed	No definition of hemoglobin response given; patients with baseline erythropoietin level > 200 IU/l had significant Hb increase from baseline to final evaluation (mean: 8.4 g/dl to 10.2 g/dl; p-value ≤? 0.001)

Appendix C. Evidence Tables

Table C66. KQ4: Serum O/P Ratio (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
Kasper 1997	Partially (sub-analysis for baseline erythropoietin level 100 IU/l	Baseline erythropoietin level ≥ 100 IU/l: 27%	Baseline erythropoietin level < 100 IU/l: 59%	Mean erythropoietin level at baseline: responder: 102.7 IU/l versus non-responder: 284.4 IU/l; p-value = 0.052		Absolute numbers could not be calculated due to missing data performance measures were therefore not calculated
Musto 1997	Yes (baseline erythropoietin O/P ratio 0.8)	O/P ratio ≥ 0.8: 1/18 (6%)	O/P ratio < 0.8: 12/19 (63%)	Not reported/assessed	Specificity: 7/24 (71%); sensitivity: 12/13 (92%); +LR: 3.2; -LR: 0.1 [positive test: O/P ratio < 0.8; target: response]	Performance measures ("Result") calculated by S.T.; ≥ 0.8 versus < 0.8: p < 0.001
Demetri 1998	No	Not applicable	Not applicable	No correlation between baseline erythropoietin level and change in hemoglobin (r = 0.017)	Not reported/assessed	Unclear what is meant by "change in hemoglobin level"; statistical methods described only inadequately
Fjornes 1998	No	Not applicable	Not applicable	Responder: median 59.0 IU/l (range 17-85); Non-responder: median 105.0 (range 74-214); p-value: 0.002	Not reported/assessed	
Glimelius 1998	Partially (sub-analysis for baseline erythropoietin level 50 IU/l and baseline erythropoietin O/P ratio 0.8 and various others; data for these not shown)	Baseline erythropoietin level > 50 IU/l: not reported; O/P ratio ≥ 0.8: 26/46 (57%)	Baseline erythropoietin level < 50 IU/l: not reported; O/P ratio < 0.8: 15/31 (48%)	Average erythropoietin levels at baseline did not differ between responders and non-responders; difference between patients with epo > 50 IU/l and epo < 50 IU/l not significant	Specificity: 16/36 (44%); sensitivity: 26/41 (63%); +LR: 1.1; -LR: 0.8 [test positive: O/P ratio ≥ 0.8; target: response]	Performance measures ("Result") calculated by S.T.; ≥ 0.8 versus < 0.8: not statistically different (no further details reported); various Epo O/P ratios tested with no statistically significant difference (no further details reported)
Oberhoff 1998	Yes (baseline erythropoietin level 50 IU/l and baseline erythropoietin O/P ratio 0.9)	Baseline erythropoietin level > 50 IU/l: 50%; O/P ratio > 0.9: 47%	Baseline erythropoietin level ≤ 50 IU/l: 46%; O/P ratio ≤ 0.9: 46%	No correlation between baseline erythropoietin level and HR	No correlation between Epo O/P ratio and HR	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; No further details reported (e.g., p-values)

Appendix C. Evidence Tables

Table C66. KQ4: Serum O/P Ratio (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
González-Barón 2002	No	Not applicable	Not applicable	Baseline erythropoietin level not significant different between responders (mean 69.1 IU/l) and non-responders (84.0 IU/l): p = n.s. and did not discriminate significantly between responders and non-responders	Not reported/assessed	No further details reported (e.g. p-value)
Hedenus 2002	Yes (baseline erythropoietin level 100 IU/l)	Not reported	Not reported	No statistically significant association between baseline erythropoietin level and hematologic response	Not reported/assessed	Epo level one of various covariates in a multiple logistic regression model
Boogaerts 2003	Yes (baseline erythropoietin level 50 IU/l; baseline erythropoietin O/P ratio 0.9)	Not reported for baseline erythropoietin level; O/P ratio ≥ 0.9 only predictive for patients with solid tumors: 27%	Not reported for baseline erythropoietin level; O/P ratio < 0.9 only predictive for patients with solid tumors: 52%	Baseline erythropoietin levels < 50 IU/l predictive for response: OR 2.5 (95%-CI: 1.2-5.1)	O/P ratio < 0.9 only predictive for patients with solid tumors: RR 1.9 (95%-CI: 1.0-3.7), p < 0.001	No further details reported; absolute numbers could not be calculated due to missing data
Cazzola 2003	Unclear	Not applicable/ reported	Not applicable/reported	Baseline erythropoietin level predictive for response: HR 0.99 (95%-CI: 0.98-1.0), p = 0.002	Not reported/assessed	Unclear if cut-off values were used; unclear if lower levels predict for response or non-response or higher levels predict for response or non-response (discussion indicates that lower levels predict for response)

Appendix C. Evidence Tables

Table C66. KQ4: Serum O/P Ratio (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum epo) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
Littlewood 2003	Yes (baseline erythropoietin level 100, 200, 300, or 500 IU/l)	> 100 IU/l: 80/145 (55%); > 200 IU/l: 29/52 (56%); 12/24% (50%); 5/12 (42%)	≤ 100 IU/l: 239/324 (74%); 290/417 (70%); 307/445 (69%); 314/457 (69%)	Baseline erythropoietin level ≤ 100 IU/l statistically related to HR in logistic regression model (p = 0.0037); specificity: 65/150 (43%); sensitivity: 239/319 (75%); +LR: 1.3; -LR: 0.6 [test positive: erythropoietin ≤ 100 IU/l; target: response]	See below	Performance measures only calculated by S.T. for the most significant cut-off (100 IU/l; authors report predictive values (positive and negative) although described as specificity and sensitivity); ≤ 100 IU/l versus > 100 IU/l: p < 0.001 (univariate analysis); ≤ 200 IU/l versus > 200 IU/l: p = 0.045 (univariate analysis); ≤ 300 IU/l versus > 300 IU/l: p = 0.052 (univariate analysis); ≤ 500 IU/l versus > 500 IU/l: p = 0.047 (univariate analysis)
Littlewood 2003	Yes (baseline erythropoietin O/P ratio 0.9)	O/P ratio > 0.9: 137/209 (66%)	O/P ratio ≤ 0.9: 125/180 (69%)	See above	Baseline erythropoietin O/P ratio ≤ 0.9 not statistically related to HR in logistic regression model	≤ 0.9 versus > 0.9: p = 0.414 (univariate analysis)
Katodritou 2004	Not reported	Not reported	Not reported	No statistically significant difference between responders and non-responders	Not reported/assessed	Univariate analysis; no further details reported (e.g. p-value)
Witzig 2004	Yes (baseline erythropoietin level 44 IU/l; 44-86 IU/l; 86 IU/l)	Data not interpretable (table labeled not unambiguously)	Data not interpretable (table labeled not unambiguously)	No difference in HR with respect to baseline erythropoietin level; p = 0.26	Not reported/assessed	Patients with HR independent of RBCT

Appendix C. Evidence Tables

Table C67. KQ4: Ferritin, Iron, Transferrin

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [ferritin] (e.g. likelihood ratio)	Result [iron] (e.g. likelihood ratio)	Result [transferrin] (e.g. likelihood ratio)	Result [transferrin saturation] (e.g. likelihood ratio)	Comments
Miller 1992	No	Not applicable	Not applicable	Ability to respond independent of baseline ferritin level (p = 0.96)	Not reported/ assessed	Not reported/ assessed	Not reported/ assessed	Different response criterion
Ludwig 1994	Yes (not reported)	Not applicable (see "Results")	Not applicable (see "Results")	Baseline ferritin level did not significantly correlate with HR	Baseline iron level did not significantly correlate with HR	Baseline transferrin level did not significantly correlate with HR	Not reported/ assessed	Point-biserial correlation
Cazzola 1995	Yes (transferrin saturation 40%)	27%	37%	Not reported	Not reported	Not reported	> 40% versus ≤ 40%: p = 0.5720 (univariate, adjusted)	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated
Henry 1995	Yes (ferritin 400 ng/ml)	Ferritin ≥ 400 ng/ml: 31/69 (45%)	Ferritin < 400 ng/ml: 46/74 (62%)	Specificity: 38/66 (58%); Sensitivity: 46/77 (60%); +LR: 1.4; -LR: 0.7 [test positive: ferritin < 400 ng/ml; target: response]	Not reported/ assessed	Not reported/ assessed	Not reported/ assessed	Performance measures ("Result") calculated by S.T.; only patients receiving chemotherapy reported here
Henry 1995	Yes (ferritin 500 ng/ml)	Ferritin ≥ 500 ng/ml: 25/62 (40%)	Ferritin < 500 ng/ml: 52/81 (61%)	Specificity: 37/66 (56%); sensitivity: 52/77 (68%); +LR: 1.5; -LR: 0.6 [test positive: ferritin < 500 ng/ml; target: response]	Not reported/ assessed	Not reported/ assessed	Not reported/ assessed	Performance measures ("Result") calculated by S.T.; only patients receiving chemotherapy reported here
Osterborg 1996	No	Not applicable	Not applicable	Not reported/ assessed	Not reported/ assessed	Not reported/ assessed	No significant predictor for HR: hazard ratio 0.92 (p-value = 0.15)	Univariate Cox's regression analysis
Kasper 1997	No	Not applicable	Not applicable	No significant difference between responder and non-responder	No significant difference between responder and non-responder	No significant difference between responder and non-responder	Not reported/ assessed	No further details reported (e.g. p-value)

Appendix C. Evidence Tables

Table C67. KQ4: Ferritin, Iron, Transferrin (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [ferritin] (e.g. likelihood ratio)	Result [iron] (e.g. likelihood ratio)	Result [transferrin] (e.g. likelihood ratio)	Result [transferrin saturation] (e.g. likelihood ratio)	Comments
Fjornes 1998	No	Not applicable	Not applicable	No significant difference between responders and non-responders	No significant difference between responder and non-responder	Not reported/ assessed	Not reported/ assessed	No further details reported (e.g. p-value)
Gonzalez 1999	Not reported	Not reported	Not reported	No significant difference between responders and non-responders	Not reported/ assessed	No significant difference between responders and non-responders	Not reported/ assessed	No further details reported (e.g. p-value)
González-Barón 2002	No	Not applicable	Not applicable	Baseline ferritin level not significant different between responders (mean 354.8 ng/ml) and non-responders (382.5 ng/ml): p = n.s. and did not discriminate significantly between responders and non-responders	Baseline serum iron level not significant different between responders (mean 79.7) and non-responders (101.4): p = n.s. and did not discriminate significantly between responders and non-responders	Baseline transferrin level not significant different between responders (mean 255.3) and non-responders (253.7): p = n.s. and did not discriminate significantly between responders and non-responders	Baseline transferrin saturation index not significant different between responders (mean 39.5) and non-responders (26.1): p = n.s. and did not discriminate significantly between responders and non-responders	No further details reported (e.g. p-value)
Littlewood 2003	Yes (ferritin 400 ng/ml)	Ferritin > 400 ng/ml: 144/231 (62%)	Ferritin ≤ 400 ng/ml: 223/310 (72%)	Baseline ferritin level ≤ 400 ng/ml statistically related to HR in logistic regression model (p = 0.0002); specificity: 87/174 (50%); sensitivity: 223/367 (61%); +LR: 1.2; -LR: 0.8 [test positive: ferritin ≤ 400 ng/ml; target: response]	Not reported/ assessed	Not reported/ assessed	See below	≤ 400 ng/ml versus > 400 ng/ml: p = 0.018 (univariate analysis)

Appendix C. Evidence Tables

Table C67. KQ4: Ferritin, Iron, Transferrin (cont'd)

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [ferritin] (e.g. likelihood ratio)	Result [iron] (e.g. likelihood ratio)	Result [transferrin] (e.g. likelihood ratio)	Result [transferrin saturation] (e.g. likelihood ratio)	Comments
Littlewood 2003	Yes (transferrin saturation 20% or 40%)	Transferrin saturation > 20%: 179/262 (68%); transferrin saturation > 40%: 58/102 (57%);	Transferrin saturation ≤ 20%: 115/172 (67%); transferrin saturation ≤ 40%: 236/332 (71%);	See above	Not reported/ assessed	Not reported/ assessed	Baseline transferrin saturation (≤ 40% or > 20%) not statistically related to HR in logistic regression model	≤ 20% versus > 20%: p = 0.75 (univariate analysis); ≥ 40% versus > 40%: p = 0.007 (univariate analysis)
Chang 2004	No	Not applicable	Not applicable	No significant predictor of response	Not reported/ assessed	Not reported/ assessed	Not reported/assessed	No further details reported (e.g. p-value)
Katodritou 2004	Not reported	Not reported	Not reported	No significant difference between responders and non-responders	Not reported/ assessed	Not reported/ assessed	Not reported/assessed	Univariate analysis; no further details reported (e.g. p-value)

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Table C68. KQ4: sTFR

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result (serum sTFR) (e.g. likelihood ratio)	Result (O/P ratio) (e.g. likelihood ratio)	Comments
Ludwig 1994	Yes (not reported)	Not applicable (see "Results")	Not applicable (see "Results")	Baseline sTFR level did not significantly correlate with HR	Not reported/assessed	Point-biserial correlation
Musto 1997	Yes (O/P ratio 0.8)	O/P ratio ≥ 0.8 1/4 (25%)	O/P ratio < 0.8: 12/33 (36%)	Not reported/assessed	Specificity: 3/24 (13%); sensitivity: 12/13 (92%); +LR: 1.1; -LR: 0.6 [positive test: O/P ratio < 0.8; target: response]	Performance measures ("Result") calculated by S.T.; < 0.8 versus ≥ 0.8: p > 0.05
Katodritou 2004	Not reported	Not reported	Not reported	No significant difference between responders and non-responders	Not reported/assessed	Univariate analysis; no further details reported (e.g. p-value)

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Table C69. KQ4: Blood count

study author	Cut-off value (value)	Type of cells	N patients responded above cut-off	N patients responded below cut-off	Result (e.g. likelihood ratio)	Comments
Miller 1992	No	Leukocytes	Not applicable	Not applicable	Ability to respond independent of baseline erythrocyte count (p = 0.66)	Different response criterion
Ludwig 1994	Yes (not reported)	Leukocytes	Not applicable (see "Results")	Not applicable (see "Results")	Baseline leukocyte count did not significantly correlate with HR	Point-biserial correlation
Littlewood 2003	Yes (2000/µl)	Leukocytes	Leukocytes > 2000/µl: 366/532 (69%)	Leukocytes ≤ 2000/µl: 16/28 (57%)	Baseline leukocyte count not statistically related to HR in logistic regression model	≤ 2000/µl versus > 2000/µl: p = 0.197 (univariate analysis)
Cazzola 1995	Yes (2000/µl)	Neutrophils	Neutrophils > 2000/µl: 37%	Neutrophils ≤ 2000/µl: 26%	Not reported	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; > 2000/µl versus ≤ 2000/µl: p = 1.0 (univariate, adjusted); according to Cox model neutrophils independent significant factor (neutrophils > 1600/µl more likely to respond)
Osterborg 1996	No	Neutrophils	Not applicable	Not applicable	No significant predictor of HR: hazard ratio 1.0 (p-value = 0.43)	Univariate Cox's regression analysis
Chang 2004	No	Neutrophils	Not applicable	Not applicable	No significant predictor of HR	No further details reported (e.g. p-value)
Miller 1992	No	Platelets	Not applicable	Not applicable	Ability to respond independent of baseline platelet count (p = 0.71)	Different response criterion

Appendix C. Evidence Tables

Table C69. KQ4: Blood count (cont'd)

study author	Cut-off value (value)	Type of cells	N patients responded above cut-off	N patients responded below cut-off	Result (e.g. likelihood ratio)	Comments
Cazzola 1995	Yes (100000/µl)	Platelets	Platelets > 100000/µl: 38%	Platelets ≤ 100000/µl: 13%	Not reported	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; > 100000/µl versus ≤ 100000/µl: p = 0.0374 (univariate, adjusted)
Ludwig 1994	Yes (not reported)	Platelets	Not applicable (see "Results")	Not applicable (see "Results")	Baseline platelet count did not significantly correlate with HR	Point-biserial correlation
Osterborg 1996	No (univariate and multivariate analysis)	Platelets	Platelets ≥ 100000/µl: titration 72%; fixed dose 68%	Platelets < 100000/µl: titration 39%; fixed dose 50%	Hazard ratio 1.2 (p-value < 0.01) (higher platelet count predicting HR)	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated; baseline platelet count was only a significant predictor in univariate analysis not in multivariate analysis
Kasper 1997	No	Platelets	Not applicable	Not applicable	Baseline platelet count did not significantly correlate with HR	There was a significant increase in reticulocytes in the first and second week in responders (p = 0.009). However, no comparison to non-responders reported
Chang 2004	No	Platelets	Not applicable	Not applicable	No significant predictor of HR	No further details reported (e.g. p-value)
Ludwig 1994	Yes (not reported)	Reticulocytes	Not applicable (see "Results")	Not applicable (see "Results")	Baseline reticulocytes count did not significantly correlate with HR	Point-biserial correlation
Garton 1995	No	Reticulocytes	Not applicable (11/20 responded	Not applicable	Mean reticulocyte counts did not differ between responders and non-responders (p = 0.06)	Very few patients

Appendix C. Evidence Tables

Table C69. KQ4: Blood count (cont'd)

study author	Cut-off value (value)	Type of cells	N patients responded above cut-off	N patients responded below cut-off	Result (e.g. likelihood ratio)	Comments
Fjornes 1998	No	Reticulocytes	Not applicable	Not applicable	No significant difference between responders and non-responders	No further details reported (e.g. p-value)
González-Barón 2002	No	Reticulocytes	Not applicable	Not applicable	Baseline reticulocyte count not significant different between responders (mean 2.7%) and non-responders (2.4%): p = n.s. and did not discriminate significantly between responders and non-responders	No further details reported (e.g. p-value)
Littlewood 2003	Yes (2.5%)	Reticulocytes	Reticulocytes > 2.5%: 117/177 (66%)	Reticulocytes ≤ 2.5%: 251/367 (68%)	Baseline reticulocyte count not statistically related to HR in logistic regression model	≤ 2.5% versus > 2.5%: p = 0.593 (univariate analysis)
Katodritou 2004	Not reported	Reticulocytes	Not applicable/reported	Not applicable/reported	No significant difference between responders and non-responders	Univariate analysis; no further details reported (e.g. p-value)

Appendix C. Evidence Tables

Table C70. KQ4: Creatinine Clearance

study author	Cut-off value (value)	N patients responded above cut-off	N patients responded below cut-off	Result [creatinine clearance] (e.g. likelihood ratio)	Result [serum creatinine] (e.g. likelihood ratio)	Comments
Cazzola 1995	Yes (0.9 mg/dl)	29%	43%	Not reported/assessed	> 0.9 mg/dl versus ≤ 0.9 mg/dl: p = 0.7190 (univariate, adjusted)	Absolute numbers could not be calculated due to losses to follow-up (unclear enumerator) performance measures were therefore not calculated
Osterborg 1996	No	Not applicable	Not applicable	Not reported/assessed	No significant predictor of HR: hazard ratio 0.99 (p-value = 0.92)	Univariate Cox's regression analysis
Musto 1997	Not reported	Not applicable/reported	Not applicable/reported	Not reported/assessed	Not reported/assessed	Presence of renal failure did not affect response to Epo
Fjornes 1998	No	Not applicable	Not applicable	Responder: median 47 ml/min (range 28-104); Non-responder: median 91 ml/min (range 59-123); p-value: 0.02	Responder: median 140.5 µmol/l (range 92-225); Non-responder: median 78.0 µmol/l (range 57-97); p-value: 0.002	
Cazzola 2003	Unclear	Not reported	Not reported	Not reported/assessed	HR 1.0 (95%-CI: 1.0-1.0), p = 0.89	Unclear if cut-off values were used

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Table C71. KQ4: Other Baseline Parameters

study author	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Comments
Ludwig 1994	C-reactive protein did not significantly correlate with HR	Interleukin-1 beta did not significantly correlate with HR	Interleukin-6 did not significantly correlate with HR	Tumor necrosis factor-alfa or -beta did not significantly correlate with HR	Neopterin did not significantly correlate with HR	Alfa1-antitrypsin did not significantly correlate with HR	Interferon-gamma did not significantly correlate with HR	Stem cell factor did not significantly correlate with HR	Point-biserial correlation
Musto 1997	Number of circulating BFU-E (median in this study = 19): BFU-E > 19: 6/9 (67%) responded; BFU-E < 19: 2/12 (17%) responded; p-value < 0.01	Interleukin-1 (median in this study = 110 pg/ml): IL-1 < 110 pg/ml: 10/16 (63%); IL-1 > 110 pg/ml: 3/21 (14%); p-value < 0.001	Interleukin-6 (median in this study = 63 IU/ml): IL-6 < 63 IU/ml versus IL-6 > 63 not statistically significant (no further details reported)	Tumor necrosis factor (median in this study = 50 pg/ml): TNF < 50 pg/ml: 11/18 (61%); TNF > 50 pg/ml: 2/19 (11%); p-value < 0.001					
Gonzalez 1999	"hemogram": no significant difference between responders and non-responders	"chemistry": no significant difference between responders and non-responders							No further details reported (e.g. p-value)
Katodritou 2004	Percentage of hypochromic erythrocytes (HYPO%): HYPO% Specificity 7/12 (60%); Sensitivity 20/20 (100%)								Multivariate analysis; cut-offs determined by ROC curve; no further details reported (e.g. p-values); absolute values derived from percentages (see brackets)

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Table C72. KQ4: Early Changes

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Ludwig 1994	Multivariate logistic regression			Response probable: serum ferritin level (absolute) < 400 ng/ml after 2 weeks: 34/47 (72%) responded; response not probable: serum ferritin level (absolute) ≥ 400 ng/ml after 2 weeks: 4/33 (12%) responded; Specificity 29/42 (69%); Sensitivity 34/38 (89%); +LR 2.9; -LR 0.2 [positive test: ferritin < 400 ng/ml; target: response]							
Ludwig 1994	point-biserial correlation	Hb increase ≥ 0.5 g/dl after 2 weeks: r = -0.55; p < 0.01	Serum erythropoietin increase after 2 weeks (no cut-off reported): r = -0.28; p < 0.01	Serum ferritin increase after 2 weeks (no cut-off reported): r = -0.32; p < 0.01	Serum neopterin increase after 2 weeks (no cut-off reported): r = -0.32; p < 0.01	Serum C-reactive protein increase after 2 weeks (no cut-off reported): r = -0.38; p < 0.01	Serum sTFR increase after 2 weeks (no cut-off reported): r = 0.34; p < 0.01	Serum transferrin increase after 2 weeks (no cut-off reported): r = 0.33; p < 0.01	Serum iron increase after 2 weeks (no cut-off reported): r = -0.33; p < 0.01	Hct increase after 2 weeks (no cut-off reported): r = 0.32; p < 0.01	Erythrocyte count increase after 2 weeks (no cut-off reported): r = 0.28; p < 0.05

Appendix C. Evidence Tables

Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Ludwig 1994	point-biserial correlation, continued	Reticulocyte count increase after 2 weeks (no cut-off reported): r = 0.28; p < 0.05	Alfa1-antitrypsin increase after 2 weeks (no cut-off reported): r = -0.23; p < 0.05	Interleukin-1 beta increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Tumor necrosis factors-alfa and -beta increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Interleukin-6 increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Interferon-gamma increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Stem cell factor increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Leukocyte increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	Platelets increase after 2 weeks (no cut-off reported) did not significantly correlate with HR	
Ludwig 1994	Stepwise discriminant analysis	Hb increase ≥ 0.5 g/dl after 2 weeks: R^2 = 0.39; p < 0.001	Serum erythropoietin level (absolute) after 2 weeks: R^2 = 0.151; p < 0.01	Serum ferritin level (absolute) after 2 weeks: R^2 = 0.14; p < 0.02							
Henry 1995	Due to losses to follow-up/missing data performance measures (spec., sens., +LR, -LR) could not be calculated; only patients receiving chemotherapy reported here	Hb increase ≥ 0.5 g/dl after 2 weeks: 34/53 (64%)	Reticulocyte count increase ≥ 40000/µl after 2 weeks: 24/41 (59%) responded		Hb increase ≥ 1 g/dl after 4 weeks: 51/70 (73%) responded	Reticulocyte count increase ≥ 40000/µl after 4 weeks: 33/46 (72%) responded					

Appendix C. Evidence Tables

Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Glaspy 1997	Hb response definition for this analysis: increase in Hb ≥ 2 g/dl over the course of Epo treatment; performance measures (Sens., Spec., +LR, -LR) calculated by S.T.				Hb increase ≥ 1 g/dl after 4 weeks: 792/1054 (75%) responded; Hb increase < 1 g/dl: 284/962 (30%) responded; specificity 678/940 (72%); sensitivity 792/1076 (74%); +LR 2.6; -LR 0.4 [positive test: Hb↑ ≥ 1 g/dl; target: response]						
Demetri 1998	No further details reported; 44% of patients with increase < 1 g/dl achieved Hb response				Hb increase ≥ 1 g/dl after 4 weeks: 81% responded						

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Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Glimelius 1998	Performance measures (Sens., Spec., +LR, -LR) calculated by S.T.; p-values reported separately for different treatment arms: 2000 IU/l: 10/17 versus 5/17 ($p < 0.05$) and 10000 IU/l: 20/21 versus 10/16 ($p < 0.05$)		Hb increase > 0.5 g/dl after 2 or 3 weeks: 30/38 (79%) responded; Hb increase ≤ 0.5 g/dl after 2 or 3 weeks: 15/33 (45%) responded; specificity: 18/26 (69%); sensitivity 30/45 (67%); +LR 2.2; -LR 0.5 [test positive: Hb increase > 0.5 g/dl; target: response]								

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Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
González-Barón 2002	Since a large amount of possible factors (early changes) were tested only significant factors in the discriminant analysis are described in detail here; no further details are given for Hb increase therefore, no performance measures (Sens., Spec., +LR, -LR) could be calculated	Factors at 2 weeks which did not significantly discriminate between responders and non-responders: RBC (absolute and increase), Hct (absolute and increase), reticulocytes (absolute and increase), serum iron (absolute and increase), ferritin (absolute and increase), transferrin (absolute and increase), transferrin saturation (absolute and increase), erythropoietin level (absolute and increase)	Factors at 4 weeks which did not significantly discriminate between responders and non-responders: RBC (absolute and increase), Hct (absolute and increase), reticulocytes (absolute and increase), serum iron (absolute and increase), ferritin (absolute and increase), transferrin (absolute and increase), transferrin saturation (absolute and increase), erythropoietin level (absolute and increase)	Discriminatory analysis and logistic regression showed that Hb (absolute) at 4 weeks and Hb increase at 4 (using a cut-off of 0.5 g/dl) weeks were the best variables in predicting response; response probable: Hb increase ≥ 0.5 g/dl after 4 weeks: predictive power 89%; response not probable: Hb increase < 0.5 g/dl after 4 weeks: predictive power 71%							

Appendix C. Evidence Tables

Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter	Parameter
Littlewood 2003	Performance measures (Sens., Spec., +LR, -LR) calculated by S.T. only for the most significant factors (Hb increase 0.3 G7dl after 2 weeks and 1 g/dl after 4 weeks)	Hb increase > 0.3 g/dl after 2 weeks: 141/186 (76%) responded; Hb increase ≤ 0.3 g/dl after 2 weeks: 149/247 (60%) responded; > 0.3 versus ≤ 0.3: p < 0.001; specificity: 98/143 (69%); sensitivity: 141/290 (49%); +LR: 1.5; -LR: 0.7 [positive test: Hb > 0.3 g/dl; target: response]	Hb increase > 0.5 g/dl after 2 weeks: 117/152 (77%) responded; Hb increase ≤ 0.5 g/dl after 2 weeks: 173/281 (62%) responded; > 0.5 versus ≤ 0.5: p = 0.001	Transferrin saturation (absolute) > 20% after 2 weeks: 34/48 (71%) responded; transferrin saturation ≤ 20% after 2 weeks: 41/60 (68%) responded; > 20% versus ≤ 20%: p = 0.779	Transferrin saturation (absolute) > 40% after 2 weeks: 10/13 (77%) responded; transferrin saturation ≤ 40% after 2 weeks: 65/95 (68%) responded; > 40% versus ≤ 40%: p = 0.553	Transferrin saturation increase > 20% after 2 weeks: 3/5 (60%) responded; transferrin saturation increase ≤ 20% after 2 weeks: 69/97 (71%) responded; > 20% versus ≤ 20%: p = 0.976	Transferrin saturation increase > 25% after 2 weeks: 2/3 (67%) responded; transferrin saturation increase ≤ 25% after 2 weeks: 70/99 (71%) responded; > 25% versus ≤ 25%: p = 1.0	Ferritin level (absolute) > 400 ng/ml after 2 weeks: 27/47 (57%) responded; ferritin level (absolute) ≤ 400 ng/ml after 2 weeks: 52/69 (75%) responded; > 400 ng/ml versus ≤ 400 ng/ml: p = 0.042	Reticulocytes increase > 0.8% after 2 weeks: 134/185 (72%) responded; reticulocytes increase ≤ 0.8% after 2 weeks: 128/210 (61%); > 0.8% versus ≤ 0.8%: p = 0.016	Hb increase > 1.0 g/dl after 4 weeks: 219/250 (88%) responded; Hb increase ≤ 1.0 g/dl after 4 weeks: 151/288 (52%) responded; > 1.0 versus ≤ 1.0: p < 0.001; specificity: 137/168 (82%); sensitivity: 219/370 (59%); +LR: 3.2; -LR: 0.5 [positive test: Hb > 1.0 g/dl; target: response]	Transferrin saturation (absolute) > 20% after 4 weeks: 83/129 (64%) responded; transferrin saturation ≤ 20% after 4 weeks: 98/134 (73%) responded; > 20% versus ≤ 20%: p = 0.124
Littlewood 2003, continued	Performance measures (Sens., Spec., +LR, -LR) calculated by S.T. only for the most significant factors (Hb increase 0.3 G7dl after 2 weeks and 1 g/dl after 4 weeks)	Transferrin saturation (absolute) > 40% after 4 weeks: 19/39 (49%) responded; transferrin saturation ≤ 40% after 4 weeks: 162/224 (72%) responded; > 40% versus ≤ 40%: p = 0.003	Transferrin saturation increase > 20% after 4 weeks: 9/18 (50%) responded; transferrin saturation increase ≤ 20% after 4 weeks: 157/221 (71%) responded; > 20% versus ≤ 20%: p = 0.062	Transferrin saturation increase > 25% after 4 weeks: 4/12 (33%) responded; transferrin saturation increase ≤ 25% after 4 weeks: 162/227 (71%) responded; > 25% versus ≤ 25%: p = 0.014	Reticulocytes increase > 0.8% after 4 weeks: 182/249 (73%) responded; reticulocytes increase ≤ 0.8% after 4 weeks: 156/246 (63%); > 0.8% versus ≤ 0.8%: p = 0.021	Transferrin saturation (absolute) > 40% after 4 weeks: 19/39 (49%) responded; transferrin saturation ≤ 40% after 4 weeks: 162/224 (72%) responded; > 40% versus ≤ 40%: p = 0.003					

Appendix C. Evidence Tables

Table C72. KQ4: Early Changes (cont'd)

Study author	Comments	Parameter	Parameter	Parameter	Parameter
Cazzola 2003	Unclear how cut-off value was determined			Hb increase ≥ 0.1 g/dl after 3 weeks: HR 1.1 (95%-CI: 1.0-1.1), p < 0.00001	
Cazzola 2003	Unclear how cut-off values were determined	sTFR increase after 2-3 weeks > 15% versus ≤ 15%: HR 1.6 (95%-CI: 1.1-2-3), p = 0.007	sTFR increase after 2-3 weeks > 20% versus ≤ 20%: HR 1.6 (95%-CI: 1.2-2-3), p = 0.003	sTFR increase after 2-3 weeks > 25% versus ≤ 25%: HR 1.7 (95%-CI: 1.2-2-3), p = 0.001	
Katodritou 2004	Multivariate analysis; cut-offs determined by ROC curve; no further details reported (e.g. p-values); absolute values derived from percentages (see brackets)	Increment of reticulocyte hemoglobin at 2 weeks (retics-Ht wk2) compared to baseline (retics-Ht wk0): retics-Ht wk2/retics-Ht wk0 ≥ 1.5: Specificity 10/12 (80%); Sensitivity 20/20 (100%)			
McKenzie 2004	Patients probably already included in Glaspy 1997 and Demetri 1998				Hb increase ≥ 1 after 4 weeks versus Hb increase < 1 after 4 weeks: Study 1: 84% vs. 47%; Study 2: 79% vs. 49%; Study 3: 80% vs. 44%; (p < 0.0001 for all)
Witzig 2004	Absolute values and performance measures (Sens., Spec., +LR, -LR) calculated by S.T. (for percentages used see brackets)	Serum ferritin level (absolute) < 400 ng/ml after 2 weeks: 50/65 (77%) responded; serum ferritin level (absolute) ≥ 400 ng/ml after 2 weeks: 16/41 (39%) responded; Specificity 25/40 (63%); Sensitivity 50/66 (76%); +LR 2.0; -LR 0.4			Hb increase ≥ 1 g/dl after 4 weeks: 48/62 (77%) responded; Hb increase < 1 g/dl after 4 weeks: 32/52 (62%) responded; Specificity 20/34 (59%); Sensitivity 48/80 (60%); +LR 1.5; -LR 0.7

Appendix C. Evidence Tables

Table C73. KQ4: Algorithms

study author	Algorithm	Result (e.g. likelihood ratio)	Comment
Ludwig 1994	Response not probable: baseline erythropoietin level ≥ 100 IU/l and Hb increase after 2 weeks < 0.5 g/dl; response probable: baseline erythropoietin level < 100 IU/l and/or Hb increase after 2 weeks ≥ 0.5 g/dl	Epo ≥ 100 IU/l and Hb↑ < 0.5 g/dl: 29/31 (94%) not responded; Epo < 100 IU/l and/or Hb↑ ≥ 0.5 g/dl: 9/45 (20%) not responded; Specificity: 36/38 (95%); Sensitivity: 29/38 (76%); +LR 14.5; -LR 0.3 [test positive: Epo ≥ 100 IU/l and Hb↑ < 0.5 g/dl; target: non-response]	Odds ratio 58.0 (95%-CI: 16.3-206.8; p < 0.000000001); multivariate logistic regression
Ludwig 1994	Response probable: baseline erythropoietin level < 100 IU/l and Hb increase > 0.5 g/dl after 4 weeks; response not probable: baseline erythropoietin level ≥ 100 IU/l and/or Hb increase ≤ 0.5 g/dl after 4 weeks	Epo < 100 IU/l and Hbc ≥ 0.5 g/dl: 15/15 (100%) responded; Epo ≥ 100 IU/l and/or Hb↑ < 0.5 g/dl: 23/61 (38%) responded; Specificity: 38/38 (100%); Sensitivity: 15/38 (39%); +LR not applicable; -LR 0.6 [test positive: Epo < 100 IU/l and Hbc ≥ 0.5 g/dl; target: response]	Odds ratio 50.8 (95%-CI: 2.9-889.1; p < 0.000001); multivariate logistic regression
Cazzola 1995	Step 1: baseline erythropoietin level ≤ 50 IU/L or erythropoietin O/P ratio ≤ 0.9 response probable if at least one criterion fulfilled. Step 2: after 2 weeks increase of Hb ≥ 0.3 g/dl response probable	Step 1: Epo ≤ 50 IU/l or O/P ratio ≤ 0.9: 30/40 responded; Epo > 50 IU/l or O/P ratio > 0.9: 1/8 responded; specificity 7/17 (41%); sensitivity 30/31 (97%); +LR 1.6; -LR 0.08 [positive test: Epo ≤ 50 IU/l or O/P ratio ≤ 0.9; target: response]; Step 2: Hb↑ ≥ 0.3 g/dl: 30/34 responded; Hb↑ ≤ 0.3 g/dl: 0/6 responded; specificity 6/10 (60%); sensitivity 30/30 (100%); +LR 2.5; -LR not applicable [positive test: Hb↑ ≤ 0.3 g/dl; target: response]	Unclear why increase in Hb at 2 weeks was chosen and how cut-off value was determined; authors report predictive values (positive and negative) although described as specificity and sensitivity; performance measures ("Result") calculated by S.T.
Henry 1995	Response probable: Hb increase ≥ 0.5 g/dl and reticulocytes increase ≥ 40000/µl after 2 weeks	Hb↑ ≥ 0.5 g/dl + ret.↑ ≥ 40000/µl: 14/21 (67%) responded; Hb↑ < 0.5 g/dl and/or ret.↑ < 40000/µl: 59/111 (53%) responded; specificity: 52/59 (88%); sensitivity: 14/73 (19%); +LR: 1.6; -LR: 0.9 [positive test: Hb↑ ≥ 0.5 g/dl + ret.↑ ≥ 40000/µl; target: response]	Performance measures ("Result") calculated by S.T.
Henry 1995	Response not probable: Hb increase < 0.5 g/dl and reticulocytes increase < 40000/µl after 2 weeks	Hb↑ < 0.5 g/dl + ret.↑ < 40000/µl: 32/62 (52%) not responded; Hb↑ ≥ 0.5 g/dl and/or ret.↑ ≥ 40000/µl: 27/70 (39%) not responded; specificity: 43/75 (57%); sensitivity: 30/57 (53%); +LR: 1.2; -LR: 0.8 [positive test: Hb↑ < 0.5 g/dl + ret.↑ < 40000/µl; target: non response]	Performance measures ("Result") calculated by S.T.
Henry 1995	Response probable: Hb increase ≥ 1 g/dl and reticulocytes increase ≥ 40000/µl after 4 weeks	Hb↑ ≥ 1 g/dl + ret.↑ ≥ 40000/µl: 27/32 (84%) responded; Hb↑ < 1 g/dl and/or ret.↑ < 40000/µl: 44/95 (46%) responded; specificity: 51/56 (91%); sensitivity: 27/71 (38%); +LR: 4.3; -LR: 0.7 [positive test: Hb↑ ≥ 0.5 g/dl + ret.↑ ≥ 40000/µl; target: response]	Performance measures ("Result") calculated by S.T.
Henry 1995	Response not probable: Hb increase < 1 g/dl and reticulocytes increase < 40000/µl after 4 weeks	Hb↑ < 1 g/dl + ret.↑ < 40000/µl: 29/45 (64%) not responded; Hb↑ ≥ 1 g/dl and/or ret.↑ ≥ 40000/µl: 27/82 (33%) not responded; specificity: 55/71 (77%); sensitivity: 29/56 (52%); +LR: 2.3; -LR: 0.6 [positive test: Hb↑ < 0.5 g/dl + ret.↑ < 40000/µl; target: non response]	Performance measures ("Result") calculated by S.T.
Glaspy 1997	Response probable: Hb increase after 4 weeks ≥ 1 g/dl and no RBCT requirement during first 4 weeks	Hb↑ ≥ 1 g/dl + no RBCT: 664/817 (81%) responded; Hb↑ < 1 g/dl and/or RBCT: 412/1199 (34%) responded; specificity: 787/940 (84%); sensitivity: 664/1076 (62%); +LR: 3.8; -LR: 0.5 [positive test: Hb↑ ≥ 1 g/dl + no RBCT; target: response]	Performance measures ("Result") calculated by S.T.
Glaspy 1997	Response not probable: Hb increase < 1 g/dl and RBCT requirement during first 4 weeks	Hb↑ < 1 g/dl + RBCT: 160/205 (78%) not responded; Hb↑ ≥ 1 g/dl and/or no RBCT: 780/1811 (43%) not responded; specificity: 1031/1076 (96%); sensitivity: 160/940 (17%); +LR: 4.1; -LR: 0.9 [positive test: Hb↑ < 1 g/dl + RBCT; target: non-response]	Performance measures ("Result") calculated by S.T.

Appendix C. Evidence Tables

Table C73. KQ4: Algorithms (cont'd)

study author	Algorithm	Result (e.g. likelihood ratio)	Comment
Fjornes 1998	Response probable: baseline erythropoietin level < 75 IU/l and serum creatinine > ULN and creatinine clearance < 60 ml/min; response not probable: baseline erythropoietin level ≥ 75 IU/l and serum creatinine ≤ ULN and creatinine clearance ≥ 60 ml/min	Epo < 75 IU/l and Crea < 60ml/min: 8/8 responded; Epo ≥ 75 IU/l and/or Crea ≥ 60 ml/min: 2/14 responded; Specificity 12/12 (100%); Sensitivity 8/10 (80%); +LR not applicable; -LR 0.2 [positive test: Epo < 75 IU/l and Crea < 60ml/min; target: response]	No details reported regarding derivation of the model (e.g. derivation of cut-off values); performance measures ("Result") calculated by S.T.
Littlewood 2003	Algorithms incorporating two or three factors (baseline parameters plus early changes) were essentially no better than single factors, i.e. change in Hb after 4 weeks		Data not reported here (12 algorithms tested/reported in Littlewood 2003)
Witzig 2004	Response not probable: erythropoietin level ≥ 100 IU/l and Hb increase after 4 weeks < 0.5 g/dl; response probable: erythropoietin level < 100 IU/l and/or Hb increase after 4 weeks ≥ 0.5 g/dl	Epo ≥ 100 IU/l and Hb↑ < 0.5 g/dl: 6/12 (50%) not responded; Epo < 100 IU/l and/or Hb↑ ≥ 0.5 g/dl: 26/92 (28%) not responded; Specificity: 66/72 (92%); Sensitivity: 6/32 (19%); +LR 2.3; -LR 0.9 [positive test: Epo ≥ 100 IU/l and Hb↑ < 0.5 g/dl; target: non-response]	This is a slightly modified version of the algorithm described by Ludwig 1994 (changes at 4 weeks instead of 2 weeks); performance measures ("Result") calculated by S.T.; HR not independent of RBCT
Witzig 2004	Response probable: erythropoietin level < 100 IU/l and Hb increase ≥ 0.5 g/dl after 4 weeks; response not probable: erythropoietin level ≥ 100 IU/l and/or Hb increase < 0.5 g/dl after 4 weeks	Epo < 100 IU/l and Hb↑ ≥ 0.5 g/dl: 43/51 (84%) responded; Epo ≥ 100 IU/l and/or Hb↑ < 0.5 g/dl: 29/53 (55%) responded; Specificity: 24/32 (75%); Sensitivity: 43/72 (60%); +LR 2.4; -LR 0.5 [positive test: Epo < 100 IU/l and Hb↑ ≥ 0.5 g/dl; target: response]	This is a slightly modified version of the algorithm described by Ludwig 1994 (changes at 4 weeks instead of 2 weeks); performance measures ("Result") calculated by S.T.; HR not independent of RBCT

Excluded Studies

Excluded at the level of full-text paper

Abbreviations/key to reasons for exclusion from analysis

cct	no randomized controlled trial
csf	CSF administered in at least one epo arm but not in control arm
data	not sufficient data available
iron	iron administered in at least one epo arm but not in control arm
low	epo dose <300 IU/kg bodyweight per week (should be specified)
mds	myelodysplastic syndrome
none	no chemo/radiotherapy
other	study objective other than a comparison of erythropoiesis-stimulating products, doses, or comparison to control; additional text provided
sct	high-dose therapy plus autologous stem cell transplantation
surg	pre- or perioperative epo administration (should be specified)
ten	≤10 patients in at least one study arm
dup	duplicate publication
exKQ1	excluded -- Key Question 1
exKQ2	excluded -- Key Question 2
exKQ3	excluded -- Key Question 3
exKQ4	excluded -- Key Question 4

plus additional free text explanations

Excluded Studies

Aapro MS, Cella D, Zagari M. Age, anemia, and fatigue. Semin Oncol 2002; 29(3 Suppl 8):55-9.exKQ1: related to Littlewood 2001

Abels R. Erythropoietin for anemia in cancer patients. Eur J Cancer 1993; 29a(Suppl 2):2-8.exKQ1: none; cct; exKQ4: data; exKQ2

Abels R. Recombinant human erythropoietin in the treatment of the anaemia of cancer. Acta Haematol 1992; 87(Suppl 1):4-11.exKQ1; exKQ2: dup Abels 1993; none; cct; exKQ4: data (no statistical methods reported)

Abels RI, Larholt K, Krantz KD, et al. Recombinant human erythropoietin (r-HuEPO) for the treatment of the anemia of cancer. Murphy MJ, editor. Alpha Medical Press, 121-141. 1991. Symp. Dayton 1991 Proc Beijing Symp, AlphaMed Press. Blood cell growth factors: present a future use in hematology and oncology. exKQ4: related to Case 1993 and Henry 1995

Adamson JW, Ludwig H. Predicting the hematopoietic response to recombinant human erythropoietin (epoetin alfa) in the treatment of the anemia of cancer. Oncology 1999; 56(1):46-53.exKQ4: review

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Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004; 22(7):1301-1307.other; different iron dosages tested, all patients received erythropoietin; exKQ4

Aziz K, Hashem T, Mobarek N, et al. Does recombinant human erythropoietin improve the outcome of radiation therapy in head and neck cancer patients. Proceedings of ASTRO Abstract #2274. 2001. cct; personal communication with author suggests that allocation was not concealed exKQ4

Balducci L. Anemia, cancer, and aging. Cancer Control 2003; 10(6):478-86.exKQ4: review article

Bamias A, Aravantinos G, Kalofonos C, et al. Prevention of anemia in patients with solid tumors receiving platinum-based chemotherapy by recombinant human erythropoietin (rHuEpo): A prospective, open label, randomized trial by the Hellenic Cooperative Oncology Group. Oncology 2003; 64(2):102-110.exKQ4: data (only transfusion requirements and Hb change reported)

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Statistical Heterogeneity

What is statistical heterogeneity, what is its effect on meta-analysis, and how should it be evaluated?

Statistical heterogeneity is "variation between trials in the underlying treatment effects being evaluated" (Higgins, Thompson, Deeks, et al., 2002) and is a consequence of clinical heterogeneity (e.g., differences among patients, interventions, outcomes) and methodological heterogeneity (e.g., differences in study designs, sources of bias).

Statistical heterogeneity among studies combined in meta-analysis may be detected if "variation in the results of the studies is above that compatible with chance alone" (Higgins, Thompson, Deeks, et al., 2002). The traditional test statistic (Cochran's Q) for evaluating heterogeneity has low power when studies are few, and may have excessive power when studies are many and large (Higgins, Thompson, Deeks, et al., 2003). A more recently-introduced test statistic, called $I^{2,}$ "describes the percentage of total variation across studies that is due to heterogeneity" (Higgins, Thompson, Deeks, et al., 2003). An I^2 value of 0% indicates no observed heterogeneity; values of 25%, 50%, and 75% are suggested to correspond with "low," "moderate," and "high" levels of heterogeneity, respectively (Higgins, Thompson, Deeks, et al., 2003).

Some degree of heterogeneity is expected since meta-analyses combine results of studies that differ to at least some degree both clinically and methodologically. "What matters is the extent to which it affects the conclusions of the meta-analysis" (Higgins, Thompson, Deeks, et al., 2003). Thus, it is important to investigate potential sources of heterogeneity for any effect on the interpretation of meta-analysis results.

In subgroup analysis, subgroup category point estimates are compared to see if they are significantly different from each other, thus identifying a potential source of heterogeneity. When more than one type of subgroup may be important, separate subgroup analyses give an incomplete and potentially misleading picture. Meta-regression can be used to test the effects of multiple subgroups at the same time (multivariate analysis) (Thompson and Higgins, 2002). Meta-regression describes an observational association across trials and should not be interpreted as derived from randomized comparisons (even though the individual trials may have been randomized). As such, meta-regression is considered an exploratory or hypothesis-generating analysis.

What information is provided by fixed-effect meta-analysis vs. random-effects meta-analysis?

Fixed-effect meta-analysis assumes that there is a common treatment effect and that variation in individual study results (described by the confidence interval around the point estimate of treatment effect) is due to chance. When there is heterogeneity that cannot be readily explained, causes of heterogeneity should be explored. Thus, a common meta-analysis protocol begins with

a fixed effect analysis, followed by an exploration of heterogeneity, whether detected statistically or logically directed by known sources of potentially significant heterogeneity.

When heterogeneity is present but cannot be explained by subgroup analysis or meta-regression, a random effects meta-analysis may be conducted. This model assumes that there are different treatment effects that follow a normal distribution. Here, the point estimate is the average of the disparate treatment effects, while its confidence interval describes the uncertainty in the location of the mean of the different treatment effects (Cochrane Reviewers' Handbook 4.2.1, http://www.cochrane.org/resources/handbook/). Thus, the result of a random-effects meta-analysis cannot be reported as an alternative estimate and variance of a fixed-effect analysis (Cochrane Reviewers' Handbook 4.2.1). Nor does a random-effects analysis discount the issue of heterogeneity; "it is always advisable to explore possible causes of heterogeneity" (Cochrane Reviewers' Handbook 4.2.1).

The use of fixed-effects versus random-effects meta-analysis is controversial. When there is no statistical heterogeneity, the results of both analyses are the same. However, the degree of heterogeneity beyond which fixed-effect results are likely to be misleading is unclear. Random-effects analyses are commonly represented as more "conservative" i.e., less-extreme point estimates and wider confidence intervals. But the random-effects assumption of a normal distribution of treatment effects may be inaccurate, with unknown effects on the result (Cochrane Reviewers' Handbook 4.2.1); random-effects analysis may also generate a result more extreme than a fixed-effect estimate, with greater statistical significance (Poole and Greenland, 1999; Engels, Schmid, Terrin, et al., 2000). Finally, a disadvantage of the random effects model is that it gives more weight to small, less precise trials (Poole and Greenland, 1999).

A review of guidelines and practice regarding statistical methods in systematic reviews reported that, "Advice was generally consistent, advocating a cautious examination of potential causes of heterogeneity and the use of random effects meta-analyses to account for variation that cannot be explained (either instead of or in addition to fixed effect analyses). Specific guidance on choosing between fixed effect and random effects meta-analyses was not [generally] available" (Higgins, Thompson, Deeks, et al., 2002).

What method of analysis was chosen for this systematic review?

The original protocol called for a fixed-effect meta-analysis followed by subgroup analysis to explore potential causes of heterogeneity. Where statistical heterogeneity was high for important patient outcomes, subgroup analysis was to be followed by meta-regression.

Clinical Trials of Erythropoietic Stimulants in Cancer (as per www.clinicaltrials.gov, searched March 2006)

Epoetin versus Darbepoetin Alfa Trials

Trial ID/Study Design	Study Title/Objective
NCT00264108 Prospective Observational	"…to evaluate the cost-effectiveness of epoetin alfa compared with darbepoetin alfa in the treatment of anemia in adults receiving chemotherapy for cancer."

Epoetin Trials

Trial ID/Study Design	Study Title/Objective
NCT00046969 Randomized Phase IV epoetin beta	"…to determine the effectiveness of epoetin beta in treating anemia in patients who are receiving cisplatin and radiation therapy for stage IIB, stage III, or stage IVA cervical cancer."
NCT00060398 Randomized Phase III epoetin alfa	"…[to study] epoetin alfa and dexamethasone to see how well they work compared to epoetin alfa alone in treating anemia-related fatigue in patients with prostate cancer that is refractory to treatment with hormone therapy."
NCT00049348* Randomized Phase II epoetin alfa	Study of more- versus less-intensive regimens for pancreatic cancer --- epoetin alfa is administered as support for the more-intensive regimen
NCT00267007** Randomized Phase II epoetin alfa	"…to evaluate the neuroprotective effect of PROCRIT® (epoetin alfa, a glycoprotein that stimulates red blood cell production) versus placebo in patients with advanced ovarian cancer who develop chemotherapy-induced peripheral neuropathy due to paclitaxel and carboplatin treatment."
NCT00258440 "Partially Randomized" Pilot Study epoetin alfa	"Determine the efficacy, in terms of maintenance of target hemoglobin and hematocrit levels, of interval dosing with epoetin alfa in treating patients with anemia undergoing chemotherapy for nonmyeloid cancer"
NCT00255749 Randomized Phase II epoetin alfa	Study in patients undergoing treatment for nonmyeloid cancer --- immediate administration of epoetin alfa versus when patient's Hb falls to 10.5 or below

*No longer recruiting patients
**Not yet recruiting patients

Darbepoetin Alfa Trials

Trial ID/Study Design	Study Title/Objective
NCT00119613 Randomized Phase III	"…to evaluate whether increasing or maintaining hemoglobin concentrations with darbepoetin alfa, when administered with platinum-containing chemotherapy in subjects with previously untreated extensive-stage small cell lung cancer (SCLC), increases survival.
NCT00058422 Phase II	"Study of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Combined With Yttrium Y 90 Ibritumomab Tiuxetan in Patients Age 60 and Over With Previously Untreated Diffuse Large B-Cell Lymphoma" --- Two of the study objectives are to determine the effect of darbepoetin alfa on 1) transfusion and hematologic response and 2) quality of life.

Darbepoetin Alfa Trials (continued)

Trial ID/Study Design	Study Title/Objective
NCT00144755 Randomized Phase III	" [to evaluate] the efficacy and safety of R-CHOP given every 14 days compared to R-CHOP given every 21 days and in association or not with darbepoetin alfa in order to maintain hemoglobin above 13 g/dl, compared to classical symptomatic treatment of anemia in patients aged from 66 to 80 years with diffuse large B-cell lymphoma."
NCT00239239 Phase II	"…to characterize the pharmacokinetics/pharmacodynamics (PK/PD) of darbepoetin alfa administered at a subcutaneous (SC) dose of 0.45 mcg/kg three times weekly (TIW) in anemic patients with non-myeloid malignancies receiving multicycle chemotherapy."
NCT00098696 Randomized Phase III	Primary objective "…to compare the efficacy of darbepoetin alfa vs placebo in reducing the occurrence of red blood cell transfusions for treatment of anemia in patients with non-myeloid cancer who are not receiving chemotherapy.
NCT00091858 Randomized Phase III	"…to evaluate the efficacy of darbepoetin alfa versus placebo in reducing the occurrences of red blood cell transfusions in subjects with anemia of cancer who are not receiving chemotherapy."
NCT00153868 Web-based Pilot Study	"… to evaluate the association between the treatment of anemia with darbepoetin alfa (aranesp) and the clinical benefits in symptom palliation, improved functional status and quality of life in patients with cancer. The feasibility of web-based assessments and data capture will be evaluated."
NCT00135317 Randomized Phase III	"…to assess if the addition of intravenous (IV) iron to 500 mcg every 3 week (Q3W) darbepoetin alfa treatment enhances response as compared to the standard practice (oral iron or no iron administration)."
NCT00261313 Phase II	"An Open Label Phase 2 Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel Delivered Every 14 Days With Pegfilgrastim and Darbepoetin Alfa Support for the Adjuvant Treatment of Women With Breast Cancer"
NCT00204633 Randomized Phase II	"…to determine the frequency of RBC transfusion in patients with metastatic "poor prognosis" germ cell tumor during high-dose chemotherapy (HD-VIP, level 6) with or without Darbepoetin alfa."
NCT00077311 Randomized Phase II	"Phase II Randomized Study of Docetaxel and Cisplatin With or Without Dimesna in Patients With Stage IIIB or IV Non-Small Cell Lung Cancer" --- In both arms, darbepoetin alfa is administered SC on day 1 of each course for hemoglobin $\leq$11 g/dL.
NCT00281892 Phase III	"…[to study] fludarabine to see how well it works when given together with or without darbepoetin alfa in treating older patients with chronic lymphocytic leukemia."
NCT00095277 Randomized Phase II	"…to demonstrate benefit with respect to hematopoietic response in subjects with anemia of cancer randomized to Darbepoetin Alfa once every 4 weeks."
NCT00058422 Phase II	"…to study the effectiveness of combining rituximab and combination chemotherapy with yttrium Y 90 ibritumomab tiuxetan in treating older patients who have B-cell lymphoma that has not been previously treated." --- darbepoetin alfa given as support therapy
NCT00144131 Randomized Phase II	"…[to] compare the efficacy (non-inferiority) of darbepoetin alfa extended dose schedule administration (EDS) versus darbepoetin alfa administered once per week (QW) in the treatment of anemia in subjects with non-myeloid malignancies receiving multi-cycle chemotherapy."

Community Studies of Epoetin and Darbepoetin

Four community studies of epoetin enrolled 8,501 patients from over 1,700 community oncology practices, of whom, 7,725 were evaluable at baseline, which was one month prior to epoetin treatment (Glaspy, Bukowski, Steinberg, et al., 1997; Demitri, Kris, Wade, et al., 1998; Gabrilove, Cleeland, Livingston, et al., 2001; Shasha, George, and Harrison, 2003). Patients in community studies are similar to those in randomized controlled trials as selection criteria for enrollment were largely the same as those used in most RCTs: undergoing chemotherapy and/or radiotherapy, Hb $\leq$11, life expectancy of at least six months. Study duration, 16 weeks, was the same as in the majority of RCTs. All community studies reported pre-post comparisons; none had a control group.

The study objective of Glaspy, Bukowski, Steinberg, et al. (1997) was to evaluate effectiveness of epoetin in a community oncology practice setting. Demetri, Kris, Wade, et al. (1998) correlated changes in quality of life measures with hemoglobin response and assessed these independent of tumor response. Gabrilove, Cleeland, Livingston, et al. (2001) and Shasha, George, and Harrison (2003) evaluated once-weekly epoetin dosing, used as an alternative to the standard three-times-weekly dosing,

These studies report that benefits of epoetin can be achieved in community oncology settings. Frequency of transfusion decreased from baseline and quality of life improved, as measured by FACT-An or linear analog scale assessment (LASA). Magnitude of effect is difficult to judge in these uncontrolled studies or to compare with that observed in RCTs. Transfusion results were reported in community studies as persons transfused per month and cannot be directly compared to the result reported in RCTs, percent of all patients transfused over the study duration.

Loss to follow-up was very high in the community studies. Pooling the four studies, the number of evaluable patients at study endpoint (four months) was 58 percent of those enrolled and 64 percent of those evaluable at baseline. In general, the most common reasons reported for loss to follow-up were death, disease progression, and failure to respond to epoetin. In contrast, few RCTs had more than 10 percent of patients not evaluable for transfusion, though loss to follow up for quality of life measures was 19 percent across studies and as high as 59 percent in one trial.

The community studies do not add to knowledge of adverse effects of epoetin. The studies generally reported adverse effects to be those expected with chemotherapy.

One community study of darbepoetin (Vadhan-Raj, Mirtsching, Charu, et al., 2003) enrolled 1,173 patients from 194 oncology practices, with 69% of patients completing the study. Patient population and study duration were similar to those in the community studies of epoetin and RCTs of darbepoetin. Study objective was to assess ability darbepoetin to correct anemia of chemotherapy and to examine the relationship between improvements in hemoglobin and changes in fatigue and functional capacity. Improvements in fatigue and function were reported to parallel rise in hemoglobin. Each treatment-related adverse event (e.g., deep vein thrombosis, myalgia, edema) reportedly occurred in fewer than 1% of subjects, except for injection site pain in 2%.