

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 02: Cancer

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists 25 topics for which (1) preliminary data from a trial intended to support regulatory approval for drugs (i.e., phase III data for most drugs and phase II data for accelerated, fast-track, or orphan drugs), phase II or III data for devices or procedures or data from pilot programs were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; *and* (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (A total of 230 topics in this priority area were being tracked in the system as of May 8, 2015). Please note that some of the comments received on some interventions predated their recent approvals by the U.S. Food and Drug Administration (FDA). For purposes of this report, we aggregated related topics for summary and discussion (i.e., by drug class and disease). Topics in this Executive Summary and report are organized alphabetically by disease state and by intervention. We present 13 summaries on 19 topics (indicated by an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 02: Cancer

Topics	High-Impact Potential
1. Ado-trastuzumab emtansine (Kadcyla) antibody-drug conjugate for treatment of advanced HER2-positive breast cancer	Prior high-impact topic (December 2014); archived April 2015
2. * Anamorelin for treatment of cancer-related cachexia/anorexia	Lower end of the high-impact-potential range
3. Bevacizumab (Avastin) for treatment-refractory ovarian cancer	No high-impact potential; archived on basis of experts’ comments
4. * Blinatumomab (Blinicyto) for treatment of acute lymphoblastic leukemia	Lower end of the high impact-potential range
5. * Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High
6. * Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma	High
7. * Ibrutinib (Imbruvica) for treatment of Waldenström’s macroglobulinemia	High
8. * Idelalisib (Zydelig) for treatment of chronic or small lymphocytic leukemia	High
9. * Idelalisib (Zydelig) for treatment of indolent non-Hodgkin’s lymphoma	High

Topics	High-Impact Potential
10. * Lenvatinib for treatment of differentiated thyroid cancer	Lower end of the high-impact-potential range
11. * Nivolumab (Opdivo) for treatment of advanced melanoma	Moderately high
12. * Nivolumab (Opdivo) for treatment of nonsmall cell lung cancer	High
13. Olaparib (Lynparza) for treatment of ovarian cancer	No high-impact potential at this time; awaiting additional data from phase III trials
14. * Ovarian tissue cryopreservation for fertility preservation in females undergoing gonadotoxic cancer therapy	Lower end of the high-impact-potential range
15. * Palbociclib (Ibrance) for treatment of estrogen receptor–positive breast cancer	Moderately high
16. * Pembrolizumab (Keytruda) for treatment of advanced melanoma	Moderately high
17. Radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases	Prior high-impact topic (December 2014); archived April 2015
18. * Ramucirumab (Cyramza) for treatment of gastric cancer	Lower end of the high-impact-potential range
19. * Ruxolitinib (Jakafi) for treatment of polycythemia vera	Lower end of the high-impact-potential range
20. * Siltuximab (Sylvant) for treatment of multicentric Castleman's disease	Lower end of the high-impact-potential range
21. * Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	Lower end of the high-impact-potential range
22. Specialized care model for adolescents and young adults with cancer	Prior high-impact topic (December 2014); archived April 2015
23. * Stool DNA molecular test (Cologuard) for colorectal cancer screening	Lower end of the high-impact-potential range
24. * Talimogene laherparepvec (T-VEC) for treatment of advanced melanoma	Lower end of the high-impact-potential range
25. Web-based education program (Preparatory Education About Clinical Trials) to increase enrollment in oncology clinical trials	No high-impact potential; archived April 2015 on basis of experts' comments

FDA: U.S. Food and Drug Administration

Discussion

Prior Potential High-Impact Topics Archived

The following three topics that were deemed to have high-impact potential in previous reports have been archived since the December 2014 Potential High-Impact Interventions Report because they no longer meet criteria for tracking in the Healthcare Horizon Scanning System. These topics have either timed out (being 2 years past FDA approval), or they have diffused broadly after tracking for more than 2 years. Two other reports that did not have high-impact potential also were archived; they are discussed in the next section.

- **Ado-trastuzumab emt ansine (Kadcyla) antibody-drug conjugate for treatment of advanced HER2-positive breast cancer:** Experts who commented thought ado-trastuzumab emtansine had significant potential to improve outcomes for patients with HER2-positive metastatic breast cancer. They thought that the shortcomings of previous therapies represented a significant unmet need. Commenters also stated that the drug's potential to displace current standard of care for HER2-positive metastatic breast cancer could have significant impacts on patient management. Because the drug is second-line therapy, it does not displace other therapy, and thus adds to costs of patient care. Commenters noted that its cost was comparable to monthly costs of other targeted cancer therapies. FDA approved ado-trastuzumab emtansine in February 2013. This drug has been diffusing for more than 2 years; therefore, it no longer meets criteria for tracking and was archived in April 2015 in the horizon scanning system.

- **Radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases:** Experts' comments indicated that radium-223 dichloride had significant potential to improve treatment for bone metastases, particularly for patients with prostate cancer. Although commenters thought radium-223 dichloride would likely be widely adopted for this indication, they thought it had similarities to other treatments that would limit the treatment's impact on the health care system infrastructure and practices. FDA approved radium-223 dichloride for treating solid tumor bone metastases in May 2013. This drug has been diffusing for more than 2 years; therefore, it no longer meets criteria for tracking and was archived in April 2015 in the horizon scanning system.
- **Specialized care model for adolescents and young adults (AYAs) with cancer:** An important unmet medical need exists for health care models focusing on the special needs of AYAs, though experts. However, some were concerned about the absence of clinical data on the impact of AYA centers on AYA health outcomes. One commenter with clinical background was concerned that this care model might lead to structural and administrative changes before evidence demonstrates that health outcomes are improved with this care model. If this model is implemented, clinicians and patients would widely accept its programs, commenters also thought. Some commenters thought the few available AYA centers would limit access to AYA care and increase health disparities while others thought it could decrease outcome disparities between AYAs and non-AYAs. Cost information about these models is not readily available. Costs incurred would include medical and social work staff trained to care for AYAs, physical environments attuned to needs of AYAs, and AYA-focused support groups, extended hours, and care coordination targeted at the mobile lifestyles of many AYAs (e.g., attending college). When this specialized care model was first identified, the U.S.-based nonprofit Teen Cancer America had established the first AYA unit in the country and was planning to develop additional centers. By 2015, at least 30 health centers throughout the U. S. had implemented an AYA care model (though not all under the auspices of Teen Cancer America); thus, this model is considered to be diffusing widely and we archived it in April 2015 in the horizon scanning system because it no longer meets tracking criteria.

Eligible Topics Not Deemed High Impact

In this section, we briefly discuss three topics that were deemed to have no high-impact potential at this time based on experts' comments, poor outcomes in clinical trials, or no longer meeting Healthcare Horizon Scanning System requirements. We archived two of these topics.

- **Bevacizumab (Avastin) for treatment-refractory ovarian cancer:** Bevacizumab for treating ovarian cancer has potential to address the unmet need, commenters opined. Three agreed patients would benefit from bevacizumab if their disease progressed after first- and second-line therapy. Among them, a clinical expert pointed out that ovarian cancer is the deadliest gynecologic cancer and any improvement in survival is important. In contrast, another clinical commenter thought the short extension in survival would not benefit patients because of potential for side effects. Despite bevacizumab offering a small increase in survival, overall, commenters thought inconsistent outcomes among different studies, an increase in adverse events (i.e., gastrointestinal perforations, hypertension), and failure to identify the population with the best response rates limit the clinical benefits of bevacizumab. FDA approved bevacizumab in November 2014 for treating recurrent platinum-resistant ovarian cancer, although it has been listed for several years in National Comprehensive Cancer Network guidelines as an off-label option for treating ovarian cancer

in the second- and third-line settings. For all of the above reasons, bevacizumab was deemed to have no high-impact potential and we archived the topic in May 2015.

- **Olaparib (Lynparza) for treatment of ovarian cancer:** Commenters thought an important need exists for treatments that can improve outcomes in patients with platinum-resistant ovarian cancer. However, commenters agreed that clinical data did not consistently show significant benefit, because olaparib extended only the time of remission, but not overall survival. Although clinicians could offer olaparib as another option for platinum-resistant ovarian cancer, its associated adverse events would probably deter patient adoption, thought experts. In December 2014, FDA approved olaparib for treating advanced ovarian cancer in patients with germline *BRCA* mutations who have received at least three chemotherapies. Despite FDA approval, the available phase III data and expert comments do not support olaparib as having high-impact potential. We await additional data from ongoing phase III trials and will then seek additional expert comments to determine whether it might have future potential for high impact.
- **Web-based education program (Preparatory Education About Clinical Trials) to increase enrollment in oncology clinical trials:** Overall, commenters agreed the Preparatory Education About Clinical Trials (PreACT) program has potential as an education tool for patients to determine whether to enter a clinical trial and to lower enrollment barriers. Only about 5% of patients with cancer participate in clinical trials; PreACT could potentially clear up misconceptions about the study and increase patient enrollment. Additionally, for many patients with advanced cancer, PreACT may increase awareness about clinical trials, which as a commenter explained, might be the only treatment option. Commenters also anticipate clinicians and patients will adopt this Web-based program to learn more about clinical trials but that health care infrastructure and patient management will remain unaffected. At the same time, commenters do not expect the program to affect disparities or increase costs. However, PreACT has many competitors in other forms, including Web sites and apps for mobile devices that also offer information about clinical trials, a commenter with a clinical perspective argued. Because PreACT does not have distinctive features that make the program stand out among various clinical trial educational options, this topic was deemed to have no high-impact potential and we archived the topic in May 2015.

Eligible Topics Deemed High Impact

Topics that emerged as having potential for high impact include novel drugs and biologics for treating various cancers; a novel colorectal cancer (CRC) screening test; and a procedure intended to preserve fertility in female cancer patients. The conditions that these interventions address include both solid tumors (breast cancer, CRC, gastric cancer, nonsmall cell lung cancer [NSCLC], melanoma, and thyroid cancer) and hematologic malignancies (Castleman's disease, acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], mantle cell lymphoma, non-Hodgkin's lymphoma, and polycythemia vera). Additionally, one intervention is intended to treat a side-effect of advanced cancer: cancer-related cachexia/anorexia. The group of therapeutic agents includes both small-molecule and biologic drugs. Most small-molecule drugs, such as a dual cyclin-dependent kinase (CDK) inhibitor, a ghrelin-receptor agonist, and five kinase inhibitors, have well-defined mechanisms of action and target a specific signaling pathway involved in cancer pathogenesis. The CDK inhibitor is a first-in-class small molecule that selectively targets CDK4 and CDK6 and has a synergistic effect with endocrine therapy to prevent proliferation of estrogen receptor-positive breast cancer. Large-molecule drugs include five monoclonal antibodies, which

target either molecules involved in hallmarks of cancer: angiogenesis (ramucirumab) and immune tolerance (nivolumab, pembrolizumab) or molecules expressed by malignant cells (CD19 [blinatumomab], interleukin-6 [siltuximab]). The eligible topics also include a first-of-its-kind oncolytic virus bioengineered to replicate in cells that are actively dividing, which is characteristic of tumor cells. The cancer screening test offers a potentially simpler or purportedly improved solution to existing technologies.

Breast Cancer

Palbociclib (Ibrance) for Treatment of Estrogen Receptor–Positive Breast Cancer

- **Key Facts:** In 2015, the American Cancer Society estimated that about 75% of the anticipated 234,000 cases of invasive breast cancer in the United States would be estrogen receptor–positive (ER-positive). This subclass is characterized by overexpression of the estrogen receptor. Some of the available treatment options inhibit ER signaling by targeting the receptor directly or blocking the pathway responsible for synthesizing the ER ligand. Although oncologists treat patients with alternating endocrine therapies to reduce the chance of drug resistance, disease recurrence occurs in a significant number of patients with ER-positive breast cancer. Therefore, a need exists for drugs targeting elements downstream of the ER pathway that have the potential to decrease the incidence of drug resistance. One of the early steps of cell proliferation is mediated by CDKs 4 and 6 when they interact with cyclin D, which in turn inactivates the tumor suppressor protein, retinoblastoma (Rb). Upon phosphorylation by the CDK4/6-cyclin D complex, Rb releases its inhibitory hold on the transcription factor E2F, which will begin to transcribe genes required for DNA synthesis, promoting cell-cycle progression. Palbociclib (Ibrance[®]) selectively inhibits CDK 4 and 6 and purportedly reduces drug resistance by blocking cell-cycle progression and inhibiting cancer cell proliferation. In February 2015, palbociclib was approved as first-line treatment for ER-positive/human epidermal growth factor receptor 2–negative (HER2-negative) breast cancer in combination with letrozole under FDA’s breakthrough therapy designation and priority review programs. Palbociclib is administered orally, daily, for 3 or 4 weeks at a dose of 125 mg, and this regimen is being studied in combination with letrozole as first-line treatment of advanced ER-positive/HER2-negative breast cancer.

Finn et al. (2015) reported results from the phase II PALOMA-1 trial that compared palbociclib plus letrozole combination with letrozole alone in treatment-naïve postmenopausal women with advanced ER-positive/HER2-negative breast cancer. They reported that palbociclib increased progression-free survival and had an improved trend in overall survival. The most common adverse events reported with palbociclib were arthralgia, back pain, diarrhea, dyspnea, fatigue, leukopenia, nausea, neutropenia, and thrombocytopenia. These findings were the basis for a new drug application (NDA), which was granted priority review by FDA. Additionally, palbociclib is being studied in the adjuvant setting and as second-line treatment in patients whose disease has progressed after different types of endocrine therapy. Results from PALOMA-3, a phase III trial testing palbociclib in combination with fulvestrant for treating endocrine therapy-relapsed advanced ER-positive/HER2-negative breast cancer, were reported by Turner et al. in June 2015. Investigators and an independent data monitoring committee determined that palbociclib plus fulvestrant significantly improved progression-free survival over placebo plus fulvestrant (9.2 vs. 3.8 months). Based on a U.S.-based, online aggregator of prescription-drug prices, GoodRx, 21 capsules of 125 mg of palbociclib costs about \$10,200. We found a

prescription formulary and a medical policy that offer coverage for palbociclib, which like other cancer drugs is categorized as a specialty pharmaceutical requiring prior authorization for coverage. Two other CDK4/6 inhibitors—abemaciclib and ribociclib—are also in development for treating breast cancer and could compete with palbociclib.

- **Key Expert Comments:** Most experts commenting, including two clinicians, believe that patients with ER-positive breast cancer survive long enough to develop recurrence and have limited second-line treatment options. Therefore, they believe palbociclib has potential to improve outcomes for these patients; however, two nonclinical research experts thought available efficacy data were not impressive. Palbociclib's oral formulation would facilitate broad adoption, thought most experts, especially because it targets a novel cell-cycle checkpoint, to alter and limit cancer development. Experts, some commenting before FDA's approval, also thought insurers would cover palbociclib if FDA approved the drug, which could decrease health disparities by offering an option for this patient population.
- **High-Impact Potential:** Moderately high

Cancer–Related Cachexia/Anorexia

Anamorelin for Treatment of Cancer-Related Cachexia/Anorexia

- **Key Facts:** Cachexia is a syndrome triggered by a chronic disease and is characterized by progressive loss of body fat and skeletal muscle. Cancer-related anorexia/cachexia syndrome (CACS) manifests in 50% to 80% of cancer patients and is responsible for 20% of deaths. Nutritional intake alone cannot reverse CACS because it is caused by abnormalities in carbohydrate, fat, and protein metabolism, which is why appetite stimulators such as megestrol acetate and glucocorticoids have had limited efficacy. Therefore, a need exists for interventions that can prevent body deterioration and restore the loss of muscle and fat. Anamorelin has an N-terminal active core that binds to the ghrelin receptor and stimulates neuroendocrine responses that enhance appetite and anabolism, potentially leading to an increase in body weight and lean body muscle mass. Thus, it is thought to have potential to improve quality of life and survival of patients by counteracting the body-wasting symptoms of CACS. The binding of anamorelin's N-terminal active core to the ghrelin receptor stimulates a neuroendocrine signaling cascade that triggers anabolism and, in turn, increases appetite to increase food intake and enable gain of body weight and lean body muscle mass. In clinical trials, anamorelin is being tested in patients with NSCLC; it is administered daily, orally, at a dosage of 100 mg for 12 weeks or until disease progression or unacceptable toxicity.

In September 2014, Temel and collaborators presented results from the phase III ROMANA 1 and 2 trials at the annual European Society for Medical Oncology Conference, in which after 12 weeks of anamorelin treatment, patients experienced a significant increase in lean body mass compared with body mass for patients receiving placebo. On the other hand, Temel's group reported no statistical difference in hand-grip strength between the two groups. Patients from these trials who are able to receive further anamorelin treatment will be enrolled in the phase III ROMANA 3 extension trial to assess the long-term safety and efficacy of anamorelin. Overall, anamorelin was well tolerated by patients, with the most common grade 3–4 adverse events being asthenia, atrial fibrillation, diabetes, dyspnea, hyperglycemia, and nausea. Since anamorelin is not FDA-approved for treating CACS, no pricing, coverage, coding, or payment information is available. However, if anamorelin is approved, it is likely to be reimbursed by third-party payers.

- **Key Expert Comments:** Even though the initial data from the phase III trials are positive and indicate anamorelin has potential to address the unmet need, four of the experts thought the data were too early to allow assessment of long-term efficacy. They argue that any benefit seen at 12 weeks is no guarantee this trend will continue beyond this point. Additionally, two of these experts pointed out that cancer-related cachexia is caused by a complex mechanism that is not fully understood; therefore, it seems unlikely anamorelin as a monotherapy would be able to alleviate all cachexia symptoms. Besides anamorelin's potential for treating cachexia, other factors such as patient education and behavior can help improve quality of life and patient outcomes, an expert noted.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Colorectal Cancer

Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

- **Key Facts:** New screening methods are highly desired that could improve the accuracy of existing noninvasive screening tests for CRC and increase the percentage of the population that undergoes recommended CRC screening. Research has demonstrated that cells undergo a number of genetic and epigenetic changes during malignant transformation, and detecting these changes may indicate a precancerous lesion or cancer. The Cologuard stool DNA test is a molecular diagnostic designed to detect such changes in colon-derived cells sloughed off the intestinal walls and secreted with stool. Investigators studied the test in a 10,000-patient trial in which patients underwent Cologuard screening, fecal immunohistochemical testing (FIT, a standard noninvasive test that detects blood in stool), and colonoscopy. Imperiale and collaborators (2014) reported that, using colonoscopy findings as the gold standard, the sensitivity of Cologuard was 92.3% for CRC and 42.4% for precancerous lesions. These results compared favorably to the sensitivity of FIT, which was 73.8% and 23.8% for CRC and precancerous lesions, respectively. However, the reported specificity of Cologuard was lower than that of FIT: 86.6% versus 94.9%.

FDA approved Cologuard as a CRC screening option in August 2014. The Cologuard test underwent a parallel review by FDA and the U.S. Centers for Medicare and Medicaid Services (CMS) so that their decisions closely coincided. In October 2014, CMS issued its final national coverage determination for Cologuard, which covers use of the test once every 3 years. More recently, several third-party payers have made positive coverage determinations for non-Medicare beneficiaries. Retail cost of the Cologuard test has been reported as \$600.
- **Key Expert Comments:** Overall, experts suggested that the large number of screening-eligible patients who are not compliant with screening recommendations and the limited sensitivity of existing noninvasive test methods represents an important unmet need that a novel noninvasive test such as Cologuard could address. However, some commenters questioned the extent to which patients would opt for Cologuard-based screening, given the relatively high cost and requirement that patients collect stool samples. Additionally, expert commenters were divided as to the extent to which Cologuard improves detection rates relative to tests based on detecting blood in stool.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Fertility Issues Associated with Gonadotoxic Cancer Therapy

Ovarian Tissue Cryopreservation for Fertility Preservation in Females Undergoing Gonadotoxic Cancer Therapy

- **Key Facts:** For pediatric and reproductive-age females with cancer, treatments can negatively and often permanently affect fertility because of the gonadotoxicity of these treatments. As the number of females surviving cancer long-term continues to grow because of improved diagnosis and treatment, fertility preservation has become an increasingly important concern for women and girls undergoing gonadotoxic therapy. Cryopreserved eggs or embryos obtained before treatment for later in vitro fertilization have been the only standard options. However, this approach is not an option for many patients (e.g., pediatric patients, patients who must initiate chemotherapy immediately). A new option to preserve fertility after cancer treatment involves ovarian tissue harvesting and cryopreservation for future reimplantation after disease remission. This option is available to both prepubertal girls and reproductive-age women and does not require the ovarian stimulation or cancer treatment delays associated with fertility treatments (e.g., hormonal therapy to mature ovarian follicles for retrieval). Ovarian tissue is typically collected in a same-day outpatient surgical procedure. The patient is given general anesthesia and the surgeon retrieves tissue either laparoscopically or through an open laparotomy. Harvested ovarian tissue is prepared for cryopreservation through either slow freezing or vitrification (i.e., rapid cooling). Once the patient completes treatment, the cryopreserved ovarian tissue, or autograft, is reimplanted with the intent of restoring ovarian function and fertility. Depending on the patient, the autograft may be placed orthotopically near the original location of the ovary, or heterotopically in a location such as the forearm or abdomen. This intervention remains in early stages of development with larger studies under way to assess the safety and efficacy of ovarian tissue cryopreservation and tissue reimplantation. Publications to date have reported more than 30 successful pregnancies in individuals who have undergone ovarian cryopreservation and subsequent ovarian tissue transplantation, which includes the first case of fertility restoration when the patient's ovarian tissue was cryopreserved before puberty. High costs are anticipated for this specialized procedure, and it is unclear whether payers will provide coverage.

An economic evaluation of fertility preservation treatments determined the procedure for cryopreserving ovarian tissue would cost approximately \$27,000. Additionally, a fertility clinic has published online the estimated fees of \$429 for physician consultation, \$445 for blood tests, \$18,000 for the laparoscopic procedure to remove ovarian tissue, \$3,133 for pathology evaluation, \$1,169 for preparing ovarian tissue, and \$325 for transporting the cryopreserved ovarian tissue to the storage facility. This brings the total cost for the procedure to \$23,501, similar to the previous estimate once storage costs are included. Additional costs for storing cryopreserved ovarian tissue vary from one private banking facility to another. Some facilities charge an initial fee ranging between \$2,000 and \$4,000 to process the sample plus \$16 to \$38 per month for storage. Other facilities charge yearly fees that range between \$350 and \$425.

- **Key Expert Comments:** Experts offered very different perspectives on the importance of the unmet need and the intervention's potential to improve health outcomes. Some experts viewed the unmet need as very important and anticipated that patients and clinicians would readily welcome a new approach for fertility preservation in female cancer patients. Others did not view fertility preservation and the ability to have children in the future as a critical

concern or unmet need. Some of the views appeared to reflect personal value judgments of individual experts about patients' ability or need to procreate after having cancer. Experts commenting on this topic were also divided in their assessment of the likelihood of this intervention being adopted. Some commenters suggested that patients and clinicians would likely opt for an intervention offering the potential to preserve fertility; other commenters suggested that the limited data on the procedure thus far and the potential for reintroducing cancer through ovarian tissue transplantation could limit adoption.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Gastric Cancer

Ramucirumab (Cyramza) for Treatment of Gastric Cancer

- **Key Facts:** Even though surgical techniques, radiotherapy, and chemotherapy are available for patients with gastric cancer, outcomes remain poor because the cancer is locally advanced or metastatic in most patients at the time of diagnosis. Researchers have reported that gastric cancer progression depends heavily on vascular and epidermal growth factor pathways, and they have focused on developing drugs that target such pathways. Standard first-line therapy usually includes a combination of fluoropyrimidine/platinum-based chemotherapy with targeted drugs. Unfortunately the cancer progresses in most cases. Vascular endothelial growth factor receptor 2 (VEGFR2) has a pivotal role in forming most blood vessels involving vascular endothelial growth factor pathways, and blocking this receptor could lead to improved outcomes in patients with advanced gastric cancer. In studying ramucirumab (Cyramza®), which is an antibody against VEGFR2, researchers have reported results from two studies using the agent as monotherapy or combination therapy with paclitaxel for treating advanced gastric cancer. The REGARD trial studied patients whose disease had progressed after chemotherapy. Results from Fuchs and co-authors (2014) for the 355-patient, placebo-controlled trial showed improved median overall survival (5.2 vs. 3.8 months), and treatment (median 4 doses) was generally well tolerated. Reported common adverse events were hypertension and diarrhea. The RAINBOW trial studied ramucirumab in combination with paclitaxel for treating gastric cancer. As reported by Wilke et al. (2014), overall survival increased by 2.27 months, but adverse events were twice as severe in the combination therapy as in the paclitaxel-alone group. These events included abdominal pain, anemia, asthenia, fatigue, hypertension, leukopenia, and neutropenia.

Basing its decision on the results from the REGARD trial, FDA approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, as monotherapy after fluoropyrimidine/platinum-based chemotherapy. Positive results from the RAINBOW trial led to a second approval, for ramucirumab in combination with paclitaxel, in November 2014. The labeling includes a boxed warning about increased risk of hemorrhage, including severe and sometimes fatal events.

Ramucirumab is administered intravenously at a dosage of 8 mg/kg every 2 weeks until disease progression or until toxicity limits further treatment. An adult of about 70 kg (154 lb) would require about 560 mg per dose. A May 2015 query of a U.S.-based, online aggregator of prescription-drug prices, GoodRx, showed costs of six vials of Cyramza 100 mg/10 mL of about \$6,300—an amount sufficient for about one treatment. A search of 11 representative, private, third-party payers that publish their coverage policies online found 6 policies regarding ramucirumab as medically necessary for treating patients

with gastric cancer or gastroesophageal junction adenocarcinoma whose disease has progressed after fluoropyrimidine/platinum–based chemotherapy.

- **Key Expert Comments:** Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer because of the limited options available. Although ramucirumab showed efficacy in patients with gastric cancer, four experts thought it has only limited potential to fulfill this need because survival was marginally increased and the benefits might not outweigh the increase in adverse events. However, two experts anticipate as researchers continue to test combinations that include ramucirumab, treatment could potentially have survival benefits longer than those reported in the latest clinical trials.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Hematologic Malignancies

Blinatumomab (Blincyto) for Treatment of Acute Lymphoblastic Leukemia

- **Key Facts:** For adult patients with recurrent or refractory ALL, prognosis is poor; median overall survival is only several months and the majority of these patients will die of their disease. No consensus on the standard of care for this patient population has been established, and substantial interest exists in novel methods for treating the disease. Blinatumomab (Blincyto®) is the first in a new class of anticancer treatments known as bi-specific T-cell engagers (BITEs), which purportedly promote the interaction of T cells with cancer cells, leading to cancer cell destruction. Topp and colleagues reported data in 2015 from a single-arm trial of blinatumomab in adult patients with recurrent/refractory B-precursor ALL. In this trial, 43% of patients (81 of 189) achieved a complete response or complete response with partial hematologic recovery within the first two cycles of blinatumomab treatment. Basing its decision on these results and using its accelerated approval pathway, FDA approved blinatumomab in December 2014 for treating patients with Philadelphia chromosome–negative, recurrent or refractory B-cell precursor ALL. Blinatumomab’s prescribing information carries a black box warning regarding the potential for severe adverse events such as cytokine release syndrome and neurological toxicities, which occurred in 2% and 11%, respectively, of patients treated with blinatumomab. Additionally, the prescribing information notes that as a condition of the accelerated approval, the potential clinical benefit of blinatumomab inferred from a rate of complete response in the single-arm trial must be confirmed in a larger randomized trial. Blinatumomab’s developer reported that blinatumomab would be priced at approximately \$178,000 for a typical patient treatment consisting of two 6-week treatment cycles.
- **Key Expert Comments:** Available treatments for ALL have significant shortcomings, representing a substantial unmet need, according to commenters. Also, given this need for novel treatments and the promising responses seen in initial trials of blinatumomab, expert comments indicated that the drug is likely to be adopted widely by both patients and physicians. However, experts also cautioned that randomized controlled trials of blinatumomab would be needed to confirm the potential clinical benefit. Additionally, as a drug given in a standard ALL treatment setting to a small number of patients, blinatumomab was not seen by expert commenters as causing significant shifts in health care infrastructure or patient management.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Ibrutinib (Imbruvica) and Idelalisib (Zydelig) for Treatment of Non-Hodgkin's Lymphomas

- **Key Facts:** B-cell non-Hodgkin's lymphomas (NHLs), such as CLL, mantle cell lymphoma, and Waldenström's macroglobulinemia often respond well to first-line therapy; however, most patients experience recurrence. In this situation, available therapies have limited efficacy. Additionally, certain molecularly defined subtypes, such as CLL harboring a deletion in the short arm of chromosome 17, respond poorly to standard therapies. New agents to treat these cancers are highly desired. Recent research has identified the kinases Btk and PI3K-delta as potential targets for treating B-cell malignancies.

Ibrutinib (Imbruvica®) is an oral, first-in-class Btk inhibitor under study for treating a wide range of B-cell malignancies. Initial data on ibrutinib came from single-arm studies, which served as the basis for early FDA approvals; in 2013, Wang and coauthors reported a 68% response rate in patients with recurrent/refractory mantle cell lymphoma; also in 2013, Byrd and coauthors reported a 71% response rate in patients with recurrent or refractory CLL; and in 2015 Treon and co-authors reported a 90.5% response rate in patients with previously treated Waldenström's macroglobulinemia. More recently, data have been reported from two randomized control studies of ibrutinib in treating CLL. In 2014, Byrd and coauthors reported results from an open-label, randomized controlled trial of ibrutinib versus the CD20 antibody ofatumumab for treating patients with recurrent/ refractory CLL. In this trial, ibrutinib significantly improved overall survival compared with ofatumumab (hazard ratio [HR], 0.434; 95% confidence interval [CI], 0.238 to 0.789; $p=0.0049$). More recently, in 2015, Chanan-Khan and coauthors reported results from a double-blind, randomized controlled trial of ibrutinib in combination with bendamustine and rituximab compared with bendamustine and rituximab alone for treating patients with recurrent/refractory CLL. In this trial, adding ibrutinib to bendamustine/rituximab resulted in a statistically significant improvement in progression-free survival (HR, 0.203; 95% CI, 0.150 to 0.276; $p<0.0001$).

FDA approved ibrutinib for four NHL indications: (1) patients with mantle cell lymphoma who have received at least one prior therapy; (2) patients with CLL who have received at least one prior therapy; (3) patients with CLL harboring a 17p deletion; and (4) patients with Waldenström's macroglobulinemia. The labeled dosage for mantle cell lymphoma is 560 mg, once daily, and for CLL and Waldenström's macroglobulinemia, 420 mg, once daily. The retail prices for ibrutinib at the mantle cell lymphoma and CLL/Waldenström's macroglobulinemia doses are about \$12,800 and \$9,500 per month, respectively.

Idelalisib (Zydelig®) is an oral, first-in-class, PI3K-delta inhibitor also under study for treating a wide range of B-cell malignancies. In results of a randomized, double-blind, placebo-controlled trial of patients with recurrent/refractory CLL, Furman and collaborators (2014) reported that adding idelalisib to standard treatment with rituximab improved both progression-free survival (85% reduction in risk of progression or death) and the overall response rate (81% rituximab plus idelalisib vs. 13% rituximab plus placebo). Results of a second randomized, placebo controlled trial comparing combined idelalisib and ofatumumab to ofatumumab monotherapy were presented by Jones and colleagues in 2015. In this open-label trial, the combination of idelalisib and ofatumumab resulted in an improvement in progression-free survival relative to ofatumumab monotherapy (16.3 vs. 8.0 months; HR, 0.27; $p<0.0001$). In results of a single-arm trial of idelalisib for treating recurrent/refractory indolent NHL reported by Gopal et al. (2014), a response rate of 57% was observed.

In July 2014, FDA approved idelalisib for treating recurrent/refractory CLL in combination with rituximab and for two forms of recurrent/refractory indolent NHL (follicular lymphoma and small lymphocytic lymphoma) as a monotherapy. The retail price for idelalisib at the recommended dose of 150 mg twice daily is about \$8,200 per month.

- **Key Expert Comments:** Overall, experts opined that a significant need exists for better and novel treatments for B-cell lymphomas and that the response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, expert commenters suggested that further confirmatory studies are needed, particularly studies comparing ibrutinib and idelalisib to alternatives. Experts noted as significant the relatively benign side-effect profiles of ibrutinib and idelalisib and their potential to be used for extended periods in treating several B-cell malignancies.
- **High-Impact Potential:** High

Ruxolitinib (Jakafi) for Treatment of Polycythemia Vera

- **Key Facts:** Polycythemia vera is a myeloproliferative neoplasm that affects approximately 100,000 people in the United States. Only one treatment for the disease is FDA approved, and an unmet need exists for novel effective therapies, particularly in patients with polycythemia vera whose symptoms are inadequately controlled by treatment with hydroxyurea. The FDA-approved drug, ruxolitinib, is an orally administered, small-molecule inhibitor of two protein kinases—Janus kinase 1 and 2—that play central roles in regulating myeloid lineages. Overactivation of Janus kinase pathway signaling has been linked to pathogenesis of polycythemia vera, and about 90% of polycythemia vera cases harbor an activating mutation in the gene encoding Janus kinase 2 (i.e., *JAK2V617F*). Use of ruxolitinib in treating patients with polycythemia vera whose disease is inadequately controlled by hydroxyurea has been studied in two phase III clinical trials: RESPONSE and RELIEF. In the RESPONSE trial, ruxolitinib compared with physician's choice of best available therapy demonstrated a significant increase in the percentage of patients achieving both hematocrit control without phlebotomy and a reduction in spleen volume of at least 35% (ruxolitinib 21% vs. best available therapy 1%; $p < 0.0001$). In the RELIEF trial, ruxolitinib compared with continued treatment with hydroxyurea demonstrated a trend towards improved symptom control, but the difference was not statistically significant. The percentage of patients achieving a 50% or greater reduction in a patient-reported symptom severity score was 43.4% in the ruxolitinib arm and 29.6% in the hydroxyurea arm ($p = 0.139$).

In December 2014, FDA approved the use of ruxolitinib for treating patients with “polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea,” making ruxolitinib the first drug to be approved for treating polycythemia vera. FDA had previously approved ruxolitinib for treating a related myeloproliferative neoplasm, myelofibrosis; therefore, ruxolitinib is already available commercially. The retail cost for 1 year of ruxolitinib treatment is about \$120,000 (or \$9,995 per month).

- **Key Expert Comments:** Ruxolitinib has potential to meet a significant unmet need, given the significant morbidity that patients with polycythemia vera experience and the lack of approved treatments, the commenters thought. A subset of commenters suggested ruxolitinib has substantial potential to improve treatments for patients with polycythemia vera, citing the efficacy demonstrated in the RESPONSE trial, the relatively benign safety profile, and the lack of existing safe and effective treatments. Conversely, other experts were more cautious regarding the drug's potential, citing the lack of a statistically significant improvement in the RELIEF trial and the high cost of the drug as potential barriers to adoption.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease

- **Key Facts:** Multicentric Castleman's disease is a rare lymphoproliferative disorder without effective treatment options. Siltuximab is a monoclonal antibody specific for interleukin-6 (IL-6), a cytokine whose upregulation is thought to underlie the pathogenesis of multicentric Castleman's disease. Treatment with siltuximab purportedly neutralizes IL-6, thereby improving disease symptoms. In results of a randomized, placebo-controlled trial reported by Wong et al. (2013), patients treated with siltuximab demonstrated significantly improved tumor and symptom response (34% siltuximab vs. 0% placebo; $p=0.0012$). Siltuximab was generally well tolerated, with similar rates of adverse events reported in both treatment and placebo arms of the trial.

In April 2014, FDA approved siltuximab for treating this disease. According to the prescribing information, siltuximab is indicated for treating patients "with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative." The drug is administered by IV infusion every 3 weeks, until disease progression, at a dosage of 11 mg/kg given over 1 hour. A May 2015 query of GoodRx showed costs of approximately \$860 for a 100 mg vial. An adult of about 70 kg (154 lb) would require about 770 mg or 8 vials at a cost of about \$7,000 per dose.

- **Key Expert Comments:** Overall, experts concurred that siltuximab has potential to fill a significant unmet need of patients with multicentric Castleman's disease, given results from the clinical trial supporting its approval and the fact that FDA has approved no other therapies for this indication. However, siltuximab's overall impact is limited by the small size of the eligible patient population, the lack of any substantial changes to patient management or health care facility infrastructure, and the preliminary nature of the data on a therapy that could potentially be taken for extended periods.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Lung Cancer

Nivolumab (Opdivo) for Treatment of Nonsmall Cell Lung Cancer

- **Key Facts:** Lung cancer is the second most common cancer diagnosed in the United States and is the leading cause of cancer death. Lung cancer will be diagnosed in an estimated 221,200 Americans and an estimated 158,040 will die of the disease in 2015. NSCLC accounts for about 75% of lung cancers and has a 5-year survival rate of 2% to 13%; thus, a need exists for interventions that can improve patient outcomes. NSCLC among other types of cancer has adapted a mechanism to avoid being detected by the immune system by activating the checkpoint pathway via programmed death-1 (PD-1). Cancer cells overexpress the ligand of PD-1 (PD-L1) and diminish the antitumor response of immune T

cells upon binding to PD-1. Nivolumab (Opdivo®) is a monoclonal antibody specific for PD-1 that prevents interaction with PD-L1, thus potentially improving patient survival by disrupting the immune tolerance signal between PD-1 and PD-L1 in the immune and tumor cells, respectively. In February 2015 and after priority review, FDA approved nivolumab for treating NSCLC that has progressed after platinum-based chemotherapy. Results from the phase III CheckMate 017 and the phase II CheckMate 063 trials were the basis for nivolumab's approval.

Spigel et al. and Paz-Ares et al. presented results from the phase III CheckMate 017 and CheckMate 057 trials at the 2015 American Society of Clinical Oncology Annual Meeting. Patients with squamous NSCLC enrolled in the CheckMate 017 trial were treated with nivolumab or docetaxel, and the nivolumab group showed a statistically significant improvement in overall survival (9.2 vs. 6.0 months), progression-free survival (3.5 vs. 2.8 months), and response rate (20% vs. 9%). Meanwhile, patients with nonsquamous NSCLC in the CheckMate 057 trial who received nivolumab had improved overall survival over patients given docetaxel (12.2 vs. 9.4 months) and improved response rate (19.2% vs. 12.4%), but not longer progression-free survival (2.3 vs. 4.2 months), which could be related to PD-L1 expression. Patients with NSCLC are treated intravenously with 3 mg/kg of nivolumab once every 2 weeks until disease progression or unacceptable toxicity. GoodRx reported a cost of \$2,500 for 100 mg of nivolumab (1 dose for a 70 kg person would be 210 mg). Third-party payers that cover nivolumab require preauthorization.

- **Key Expert Comments:** Overall, most experts commenting on this intervention thought nivolumab has significant potential to improve outcomes in patients with NSCLC, who currently have limited treatment options. One expert opined that if results from additional studies are favorable and the role of PD-L1 in cancer is better understood, nivolumab has a very high potential to become a standard of care. Experts anticipate nivolumab will be adopted by both physicians and patients. Because it is administered intravenously, nivolumab will not affect health care infrastructure or patient management. The onset of serious adverse events caused by immunotherapy could be a hurdle for adoption, some experts thought. Additionally, experts also agreed nivolumab is very expensive and has a high potential to impact health care costs; whether cost will be absorbed mostly by third-party payers or patients remains to be determined.
- **High-Impact Potential:** Higher end of the high-impact-potential range

Skin Cancer

PD-1 Immune Checkpoint Inhibitors Nivolumab (Opdivo) and Pembrolizumab (Keytruda) for Treatment of Advanced Melanoma

- **Key Facts:** A medical need exists for novel treatments for advanced melanoma, because despite advances in melanoma therapies, outcomes are poor. Researchers have demonstrated that several types of cancer have developed mechanisms to evade the cellular immune response, in particular the cytotoxic response involving T cells. Under normal conditions, immune cells use these so-called immune checkpoints to prevent exacerbated immune responses, which could lead to damage of neighboring tissues and organs. A promising melanoma-treatment approach involves immune-system checkpoint inhibitors, which prolong the patient's immune cytotoxic T-lymphocyte response, targeting and killing cancer cells. Even though ipilimumab, an antibody against CTLA-4, has shown durable immune responses in some patients, such response is limited to a small number of patients. Additionally, researchers have shown high expression of the programmed death-1 (PD-1)

ligand in cancer cells, a biomarker also involved in suppressing the immune response in patients with melanoma. Researchers are studying the PD-1-specific antibodies, nivolumab (Opdivo®) and pembrolizumab (Keytruda), as treatment for advanced melanoma. The drug class is also under study for NSCLC, gastric cancer, blood cancers, and cancers of the breast, head and neck, and urothelial tract.

Nivolumab. Weber et al. (2014) presented results from a phase III trial in which patients with ipilimumab-refractory, advanced melanoma had an objective response rate of 32% with nivolumab, which was significantly greater than the response rate in patients receiving chemotherapy. Robert et al. (January 2015) reported findings from a second phase III trial that compared nivolumab with dacarbazine in previously untreated patients with advanced melanoma. Treatment with nivolumab showed an improvement in overall survival and progression-free survival, compared with dacarbazine. Additionally, Larkin et al. (2015) published results from a third phase III trial, in which the efficacy and safety of nivolumab plus ipilimumab was compared with those drugs as monotherapies. Published results showed the combination improved progression-free survival but was also associated with a higher rate of treatment-related adverse events. The most common nivolumab-related adverse events were fatigue, pruritus, and nausea.

Pembrolizumab. In results from a 135-patient, placebo-controlled trial of pembrolizumab, the highest response rate was observed in 52% of patients with advanced melanoma who were treated with 10 mg/kg of the drug every 2 weeks. In this trial, Hamid and colleagues (2013) found no statistical significance in the response rate between patients treated with pembrolizumab who had received prior ipilimumab treatment and those who had not. The most common adverse events associated with pembrolizumab treatment were fatigue, rash, pruritus, and diarrhea and were observed in 79% of patients. Similarly, results from the phase III KEYNOTE-006 trial reported by Robert et al. (April 2015) demonstrated that two different regimens of pembrolizumab improved the rates of progression-free survival and overall survival, as compared with standard treatment with ipilimumab. These observations led an independent data monitoring committee to recommend stopping the trial early.

FDA approved nivolumab in December 2014 under its accelerated approval program for treating patients with advanced melanoma after treatment with ipilimumab or a BRAF inhibitor. In September 2014, FDA approved pembrolizumab for treating ipilimumab-resistant metastatic melanoma. According to an online aggregator of prescription-drug prices, the cost of nivolumab is about \$2,500 for a 100 mg vial, while the cost of pembrolizumab is about \$6,600 for three 50 mg vials (it is also available through an expanded-access program). Nivolumab and pembrolizumab are listed on many third-party payers' formularies as specialty pharmaceuticals that require prior authorization for use.

- **Key Expert Comments:** Both nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma treatment, some experts thought. They attributed their reasoning to scarce safety and efficacy data and a similar mechanism of action to that of other approved and soon-to-be-approved melanoma therapies. However, expert clinicians regarded these checkpoint inhibitors as having high-impact potential to fulfill the unmet need because they can be used as second-line treatment in patients with very poor prognosis whose disease has progressed after treatment with ipilimumab or BRAF inhibitors. Checkpoint inhibitors could be used for treating melanoma as well as other types of cancer, a clinician noted, which could increase the potential of nivolumab and pembrolizumab to address an unmet need.

- **High-Impact Potential:** Moderately high

Talimogene Laherparepvec (T-VEC) for Treatment of Advanced Melanoma

- **Key Facts:** Advanced or metastatic melanoma is usually associated with poor patient outcomes. Despite the availability of approved treatment options for these patients, response is limited because of drug resistance developed by cancer cells; thus, an unmet need exists for novel treatments for melanoma. Talimogene laherparepvec (T-VEC) is a herpes virus bioengineered to no longer express the neurovirulence genes *ICP34.5* and *ICP47*. Deleting these factors allows T-VEC to selectively replicate in cancer cells and increase their antigen presentation, both of which purportedly kill cancer cells without affecting normal cells. Additionally, T-VEC also expresses granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that helps recruit cells that initiate the immune response against pathogens and cancer cells. In a phase II trial, Kaufman et al. (2010) demonstrated that patients treated with T-VEC had more melanoma-specific T cells than did patients treated with GM-CSF alone. Because of its novel mechanism of action, T-VEC could be less likely to lead to drug resistance, which gives it the potential to address this medical need. T-VEC is being tested in the phase III OPTiM/Study as treatment for unresectable stage IIIB, IIIC, or IV melanoma, in which patients are treated per lesion with up to 4 mL (10^6 pfu/mL) of T-VEC; after 3 weeks of rest, patients receive followup doses at a concentration of 10^8 pfu/mL, biweekly. Kauffman et al. (2014) reported a significant increase in durable response rates in patients treated with T-VEC compared with such rates in patients who were treated with only GM-CSF. Although overall survival was not statistically significant, it had a favorable trend towards treatment with T-VEC.

The results from this study were the basis for a biologics license application that Amgen submitted to FDA in July 2014. Like other oncology drugs, T-VEC is expected to be expensive and if approved by FDA, third-party payers will likely offer coverage for its FDA-approved indication as a specialty pharmaceutical requiring prior authorization.

- **Key Expert Comments:** Experts commenting on this intervention had differing opinions. Some experts thought T-VEC could address a medical need, because as a genetically engineered virus, it has the potential to improve outcomes by targeting cancer through a mechanism that differs from standard therapies. They also thought that as the first oncolytic virus to show efficacy against cancer, it could lay the groundwork for developing more efficacious interventions. Although a clinician concurs T-VEC can address an unmet need, this expert also believes its potential can increase dramatically if used in combination with another immunotherapy. Conversely, some experts thought that T-VEC does not have the potential to address an unmet need, because of the limited clinical data and because overall survival was not statistically significant. In terms of its adoption, being first of its kind could hinder T-VEC's adoption unless safety and efficacy are clearly demonstrated in future studies.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Thyroid Cancer

Multikinase Inhibitors Lenvatinib (Lenvima) and Sorafenib (Nexavar) for Treatment of Differentiated Thyroid Cancer

- **Key Facts:** The majority of diagnosed thyroid cancers are of the differentiated subtype, which is typically amenable to treatment with radioactive iodine. However, some differentiated thyroid cancers develop resistance, and when this occurs, limited treatment

options exist and prognosis is poor. Researchers have been investigating the use of targeted therapies, which are thought to regulate cancer-related processes such as cell growth, cell proliferation, cell survival, and angiogenesis. The targeted therapies that have been most extensively studied to date are the orally administered multikinase inhibitors lenvatinib (Lenvima™) and sorafenib (Nexavar®). These tyrosine kinase inhibitors have activity against multiple kinases, including VEGFR2, VEGFR3, RET, and BRAF. The tyrosine kinases targeted by these inhibitors purportedly regulate several cellular processes of tumor growth and angiogenesis; therefore, inhibiting these kinases may be of clinical benefit to patients. Specifically, the activity of lenvatinib and sorafenib against RET may be of particular importance in treating thyroid cancer, because RET has been observed in differentiated thyroid cancers. Besides RET, BRAF is also a sorafenib target, suggesting that activating mutations in these kinases may play a role in the pathogenesis of the disease. Both lenvatinib and sorafenib have been studied in phase III trials comparing the multikinases with placebo in patients with progressive, radioactive iodine–refractory, differentiated thyroid cancer. Schlumberger and collaborators (2015) demonstrated an improvement in progression-free survival in patients treated with lenvatinib, as compared with placebo (18.3 vs. 3.6 months). Similarly, Brose and colleagues (2013) also reported that sorafenib extended progression-free survival by 86% (10.8 vs. 5.8 months for placebo).

Based on the above data, NDAs for both lenvatinib and sorafenib were submitted to FDA. Lenvatinib and sorafenib were FDA-approved in February 2015 and in November 2013, respectively, for the same indication—treating radioactive iodine–refractory thyroid cancer. Sorafenib is also approved by FDA for treating patients who have advanced renal cell carcinoma or advanced hepatocellular carcinoma, and some off-label prescribing of sorafenib for treating thyroid cancer took place before the approval for the thyroid indication. Several third-party payers already had policies in place that consider lenvatinib medically necessary for treating thyroid cancer. Coverage is anticipated to continue to expand in the wake of the FDA approval. Based on a query of GoodRx, ninety 24 mg capsules of lenvatinib cost approximately \$14,300 (the daily oral dose is 24 mg). Meanwhile, the retail cost for sorafenib at a dose of 400 mg twice daily is about \$12,600 per month. The use of multikinase inhibitors may significantly add to the cost of care for patients with advanced, radioactive iodine–refractory thyroid cancers. The manufacturers offer several financial assistance options through E.A.S.Y™ and REACH®, patient-assistance programs for patients prescribed lenvatinib and sorafenib, respectively.

- **Key Expert Comments:** Although they do not provide a complete cure, both lenvatinib and sorafenib are capable of partially treating and stabilizing radioactive iodine–refractory thyroid cancer, as demonstrated by clinical results, opined some experts commenting on these interventions. Basing their opinions on improved progression-free survival data, most of the experts considered lenvatinib and sorafenib to have potential to improve outcomes in patients. A head-to-head comparison between the two drugs has not been performed, some experts noted; such studies could help determine which agent would benefit patients more. Most experts also noted that lenvatinib treatment increased incidence of adverse events, which during the trial caused clinicians to lower patient doses or prematurely discontinue treatment. The magnitude of the drugs' impact is lessened by the relatively small number of patients who would be eligible for the treatment and the oral administration route, which reduces any potential impact on health care staffing or infrastructure.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Breast Cancer Intervention

Palbociclib (Ibrance) for Treatment of Estrogen Receptor–Positive Breast Cancer

Unmet need: The American Cancer Society estimates that in 2015, more than 234,000 cases of invasive breast cancer will be diagnosed in the United States.¹ In 75% of diagnosed breast cancers, tumor cells express high levels of the estrogen receptor, which is called estrogen receptor–positive (ER-positive) disease. Therapeutic alternatives for patients with ER-positive breast cancer are drugs that inhibit ER signaling directly or inhibit the pathway responsible for synthesizing estradiol, the ER ligand. To reduce the chance of drug resistance, oncologists suppress the estrogen-signaling pathway by treating patients with alternating drug regimens. Despite taking such precautions and observing a strong response to treatment, drug resistance still develops and a significant number of patients with ER-positive breast cancer die of the disease.² A need exists for drugs targeting elements downstream of the estrogen-signaling pathway with the potential to reduce the incidence of drug resistance.

Cyclin-dependent kinases (CDKs) 4 and 6 and cyclin D are such downstream elements—they are key proteins in the cell cycle required for initiating DNA synthesis.^{3,4} Like other types of cancer, ER-positive breast cancer cells frequently have overactivated CDK 4 and 6 and overexpressed cyclin D. Palbociclib reportedly targets and selectively inhibits CDKs 4 and 6 to block cell-cycle progression and inhibit proliferation of tumor cells.^{3,5} Several phase III trials are testing palbociclib in several ER-positive breast cancer treatment settings.⁶

Intervention: A hallmark of cancer is excessive cell growth caused by uncontrolled progression through the cell cycle. This growth cycle is a stringently controlled process consisting of several phases (G0, G1, S, G2, and M) during which a cell duplicates its DNA and divides into two daughter cells.^{2,3} To prevent uncontrolled cell proliferation, cells have highly regulated checkpoints that inhibit cell-cycle progression unless conditions for DNA replication and cell division are favorable. Cell-cycle checkpoints are regulated by CDKs paired with cyclins, which drive progression from G1 to S phase and G2 to M phase. A key regulator of the G1-to-S transition is the tumor suppressor retinoblastoma (Rb). Rb's main role involves binding to the transcription factor E2F and preventing it from activating genes required for DNA replication.^{2,3} Cyclin D interacts with CDK4 and CDK6, forming complexes responsible for initiating the transition from G1 to S phase by phosphorylating Rb, which releases E2F and allows genes involved in DNA replication to be transcribed.^{3,7} Therefore, agents targeting the activity of CDK4 and CDK6 have the potential to limit cell-cycle progression.

First-generation CDK inhibitors were nonselective, inhibiting CDK4 and CDK6 as well as other CDKs. They required extended treatment sessions, which increased off-target side effects. In part because of these shortcomings, only one CDK inhibitor, palbociclib, has been approved by the U.S. Food and Drug Administration (FDA). Unlike its predecessors, palbociclib was developed to target the CDK4- and CDK6-cyclin D complexes, blocking the complexes' kinase activity and preventing Rb from becoming phosphorylated.⁷

ER-positive breast cancer cells may be particularly sensitive to CDK 4/6 inhibition.³ In luminal breast cells, progesterone and estrogen drive cell proliferation by binding to progesterone receptor (PR) and ER respectively. In ER-positive breast cancer, the ER receives signals from estrogen that promote tumor growth, even though PR may or may not be present. Endocrine therapy is the standard treatment for nonresectable ER-positive breast cancer. It includes interventions that target ER activity (e.g., tamoxifen, fulvestrant, toremifene) or aromatase inhibitors (e.g., exemestane, anastrozole, letrozole) that target estrogen synthesis. Endocrine therapy has been shown to be an effective treatment for ER-positive breast cancer, with manageable side effects; however, up to 50%

of patients with ER-positive breast cancer will develop endocrine-therapy resistance.⁸⁻¹⁰ Studies have shown cyclin D is crucial for estrogen-induced cell proliferation, which could explain why amplification of the cyclin D gene occurs in 15% to 20% of breast cancers and why cyclin D overexpression is associated with poor clinical outcomes.³ Also, gene-expression profiles have identified CDK6 overexpression to be associated with fulvestrant resistance in breast cancer cells.⁸ Inhibiting this step of the cell cycle by targeting CDKs has the potential of decreasing ER-mediated cell proliferation in breast cancer.

Because of its specificity, palbociclib is well tolerated in patients and can be combined with endocrine therapy to increase treatment efficacy and decrease drug resistance. In clinical trials, palbociclib is administered orally to patients at a dosage of 125 mg, daily, in 28-day cycles with 21 days on treatment followed by 7 days off.¹¹⁻¹⁴

Clinical trials: Palbociclib is being tested primarily as first-line treatment of locoregionally recurrent or metastatic ER-positive/human epidermal growth factor receptor 2–negative (HER2-negative) breast cancer in combination with letrozole in postmenopausal women.^{11,15} Results from the PALOMA-1 trial, a phase II randomized, open-label, placebo-controlled trial of 165 patients, were presented at the 2014 Association for Cancer Research Annual Meeting.¹⁶ Patients were treated with palbociclib (125 mg daily, for 3 out of 4 weeks) and letrozole (continuous 2.5 mg daily) or letrozole alone. PALOMA-1 met its primary endpoint of improving progression-free survival as determined by investigator assessment (20.2 months with palbociclib plus letrozole vs. 10.2 months with letrozole alone; hazard ratio [HR], 0.49; $p < 0.0004$). In January 2015, the final analysis of progression-free survival based on the cancer's biomarker status was published in *Lancet Oncology*. Cohort 1 enrolled patients who had ER-positive/HER2-negative biomarker status while cohort 2 included patients who also had cyclin D1 amplification and loss of p16. Progression-free survival significantly improved in patients who received palbociclib plus letrozole (Cohort 1, 26.1 months with palbociclib plus letrozole vs. 5.7 months with letrozole alone; HR, 0.299; $p < 0.0001$; Cohort 2, 18.1 months with palbociclib plus letrozole vs. 11.1 months with letrozole alone; HR, 0.508; $p < 0.0046$).¹⁷ Also, analysis of 61 events demonstrated an overall survival in favor of palbociclib plus letrozole (37.5 months with palbociclib plus letrozole vs. 33.3 months with letrozole alone; HR, 0.81; $p < 0.2105$).¹⁶

Palbociclib was relatively well tolerated by patients. In the PALOMA-1 trial, grade 3 or 4 adverse events occurred more often with the palbociclib plus letrozole combination than with letrozole alone. The most common grade 3 or 4 adverse events included the following:¹⁷

- Neutropenia (54% in the combination-therapy group vs. 1% in the letrozole-alone group)
- Leukopenia (19% vs. 0%)
- Anemia (6% vs. 1%)
- Diarrhea (4% vs. 1%)
- Dyspnea (4% vs. 1%)
- Fatigue (4% vs. 1%)
- Nausea (2% vs. 1%)
- Thrombocytopenia (2% vs. 0%)
- Arthralgia (1% vs. 3%)
- Back pain (1% vs. 1%)

Palbociclib is also being tested as second-line treatment in combination with fulvestrant, an ER antagonist, in patients who have failed endocrine therapy (PALOMA-3) or in combination with exemestane, a steroidal aromatase inhibitor, in patients whose disease has progressed after treatment with nonsteroidal aromatase inhibitor (PEARL).^{13,14} At the 2015 American Society of Clinical Oncology (ASCO) annual meeting, Turner and collaborators presented results from PALOMA-3, a

placebo-controlled, parallel-assignment phase III trial of 521 patients with advanced ER-positive/HER2-negative breast cancer who were randomly assigned in a 2:1 ratio to receive palbociclib (125 mg, daily orally for 3 weeks out of a 4-week cycle) plus fulvestrant (500 mg, intramuscularly on days 1 and 15 of cycle 1, and then on day 1 of each subsequent 4-week cycle) or placebo plus fulvestrant. The combination of palbociclib with fulvestrant improved progression-free survival of patients, as compared with placebo plus fulvestrant (9.2 vs. 3.8 months; HR, 0.42; $p < 0.001$).¹⁸ In April 2015, the manufacturer announced the PALOMA-3 trial was stopped early because an independent data monitoring committee confirmed a significant improvement in progression-free survival in women who were treated with palbociclib plus fulvestrant.¹⁹ The most common grade 3 or 4 palbociclib plus fulvestrant-related adverse events were very similar to those manifested with palbociclib plus letrozole reported in PALOMA-1 and included the following:¹⁸

- Neutropenia (62.0% with palbociclib plus fulvestrant vs. 0.6% with placebo plus fulvestrant)
- Leukopenia (25.2% vs. 0.6%)
- Anemia (2.6% vs. 1.7%)
- Thrombocytopenia (2.3% vs. 0%)
- Fatigue (2.0% vs. 1.2%)
- Febrile neutropenia (0.6% vs. 0.6%)

Also, palbociclib is being studied as an adjuvant in combination with endocrine therapy in patients who are at risk of breast cancer recurrence after surgical resection (PENELOPE-B).¹²

Manufacturer and regulatory status: Pfizer, Inc. (New York, NY), is developing the dual CDK4/6 inhibitor palbociclib. In February 2015, basing its action on results from the phase II PALOMA-1 trial and using its accelerated approval pathway, FDA approved palbociclib under its breakthrough therapy designation and priority review programs for use in combination with letrozole for treating advanced ER-positive/HER2-negative breast cancer in the first-line setting.^{4,20}

Diffusion and cost: A U.S.-based, online aggregator of prescription-drug prices, GoodRx, listed costs as of May 2015 of about \$10,200 for 21 capsules of palbociclib 125 mg.²¹ Eligible patients who are uninsured or underinsured can receive free palbociclib for up to 12 months through Pfizer's RxPathways™ program.²² The U.S. Centers for Medicare & Medicaid Services has not issued a national coverage determination for palbociclib. Thus, coverage decisions are left to the discretion of local Medicare carriers. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found a formulary and a policy that cover palbociclib for treating ER-positive/HER2-negative breast cancer; like other orally administered anticancer drugs, it is classified as a specialty pharmaceutical and requires prior authorization for coverage.^{23,24} Drugs intended to treat patients in whom cancer has been diagnosed are typically covered for their FDA-approved indications. Therefore, once policies for palbociclib are updated, additional third-party payers will likely cover its use for treating ER-positive/HER2-negative breast cancers.

Clinical Pathway at Point of This Intervention

The majority of palbociclib studies are assessing the drug's activity in patients undergoing systemic treatment for locally advanced or metastatic breast cancer. Patients with locally advanced or metastatic ER-positive breast cancer are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens and may undergo multiple rounds of endocrine therapy. Typically patients are first treated with a nonsteroidal aromatase inhibitor (i.e., anastrozole, letrozole). Upon disease progression, patients may be switched to another class of endocrine therapy, often a steroidal aromatase inhibitor (e.g., exemestane) or an ER antagonist (e.g., fulvestrant, tamoxifen).

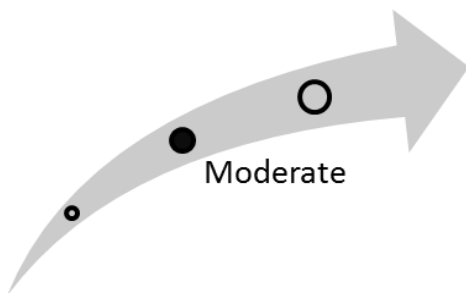
More recently, studies have demonstrated improved outcomes with combination therapy using exemestane and the mTOR inhibitor everolimus in patients whose disease has progressed after nonsteroidal aromatase inhibitor treatment. Besides endocrine therapies, various cytotoxic chemotherapy regimens may be prescribed; these regimens are typically reserved until patients have tried several endocrine therapies.²⁵ Palbociclib is under study as a complementary or competing intervention to these options in the following trials:

- The PALOMA-1 and PALOMA-2 trials are studying palbociclib in combination with the aromatase inhibitor letrozole in first-line endocrine treatment
- The PALOMA-3 trial is studying palbociclib in combination with the ER antagonist fulvestrant in patients who have received endocrine therapy
- The PEARL trial is studying palbociclib in combination with the steroidal aromatase inhibitor exemestane in patients whose disease has become resistant to a nonsteroidal aromatase inhibitor

Also, endocrine therapy may be used in the adjuvant setting to reduce the risk of breast cancer recurrence in patients who have undergone surgical resection as treatment for localized breast cancer.²⁵ In this setting, palbociclib is being studied in combination with standard endocrine therapy in patients at high risk of breast cancer recurrence (PENELOPE-B trial).

Besides palbociclib, other CDK4/6 inhibitors (e.g., abemaciclib, ribociclib) are also under study for treating breast cancer and could eventually compete with palbociclib.⁷

Figure 1. Overall high-impact potential: palbociclib (Ibrance) for treatment of advanced estrogen receptor-positive breast cancer



Most experts commenting on this intervention agree that patients with ER-positive breast cancer survive long enough to develop recurrence and have limited second-line treatment options. Therefore, they believe palbociclib has moderately high potential to improve outcomes for these patients. However, a subset of experts thought palbociclib's potential to address the unmet need is small, basing their assessment on the lack of efficacy data thus far. The experts noted that broad adoption of palbociclib could be facilitated by its oral formulation and fact that it targets a novel cell-cycle checkpoint responsible for cancer development. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health technology, and health systems backgrounds, offered perspectives on the topic of palbociclib for treating ER-positive breast cancer.²⁶⁻³¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for novel agents targeting elements downstream of the ER that can reduce the incidence of drug-resistant breast cancer, the experts thought. But targeting the Rb pathway by inhibiting CDK4 and 6 might not be the best approach to

address the unmet need, one expert thought.³¹ Most experts believe palbociclib has the potential to improve outcomes because it is being tested under various conditions, even if current clinical data do not show significant improvement. Therefore, they thought, subsequent trials are required to confirm results from early trials and demonstrate improvement in overall survival

Acceptance and adoption: Both physicians and patients would be likely to adopt palbociclib, experts suggested, because of its oral route of administration and potential to increase progression-free survival. Two experts thought results from the ongoing phase II trial did not successfully demonstrate that benefits outweigh the increased incidence of adverse events.^{29,31} However, two clinicians believe patients with progressive ER-positive breast cancer will choose to receive treatment, despite side effects, in particular if it improves patient outcomes.^{27,30}

Health care delivery infrastructure and patient management: Experts anticipated that as an orally administered medication, palbociclib would not significantly shift health care staffing or infrastructure. Also, patient management would not require significant changes; after an oncologist prescribes palbociclib, the patient will continue daily treatments from home and would be monitored frequently for side effects.

Health disparities: Palbociclib has small to moderate potential to affect health care costs, experts anticipated. Although palbociclib was not FDA approved and had no specific cost information at the time experts made their comments, they assumed it would be priced similarly to other cancer drugs. However, with demonstrated efficacy and FDA approval, it would likely be covered as a specialty drug requiring prior authorization, thought experts. Overall, palbociclib has small potential to affect health disparities, opined experts. Two experts, in particular, believe palbociclib will disseminate among patients with low socioeconomic status, because this group is more likely to have access to oral medications such as palbociclib than intravenously administered drugs.^{26,27} A caveat is that if palbociclib gains wider approval as a second-line treatment, many low-income patients may not receive intravenous (IV) infusion with first-line treatments and may be limited in their access to palbociclib.

Cancer-Related Cachexia/Anorexia Intervention

Anamorelin for Treatment of Cancer-Related Cachexia/Anorexia

Unmet need: Chronic diseases, such as cancer, can cause involuntary weight loss known as cachexia in patients. In cancer-related anorexia/cachexia syndrome (CACS), skeletal muscle and body fat is gradually lost and continues to deteriorate as the disease progresses.³² Morbidity and mortality increases in patients who develop CACS; the condition occurs in 50% to 80% cancer cases and accounts for 20% of deaths in patients with cancer.^{33,34} Although some CACS treatments, such as megestrol acetate and glucocorticoids, can decrease muscle deterioration and weight loss, they have limited efficacy and have not been shown to improve survival.³⁵ A need exists for novel agents that can prevent CACS-mediated deterioration and improve patient outcomes. Anamorelin is an oral ghrelin-receptor agonist capable of enhancing appetite and increasing anabolism. Anamorelin is purported to counteract the body-wasting symptoms in patients with CACS and has the potential to increase survival and improve quality of life.³³

Intervention: The biggest challenge for patients with CACS is that their loss of weight and lean muscle mass cannot be reversed by nutritional intake alone. Because it is caused by an alteration in the patient's metabolism, investigators believe that cachexia/anorexia treatment needs to correct the patient's metabolism rather than the patient's food intake.³²

Clinicians have observed an increase in ghrelin levels in patients with CACS, and it is assumed this increase occurs in response to decreases in food intake, lean muscle mass, and weight.³⁴ Ghrelin is a gastric hormone that is widely expressed throughout the body. It consists of an octanoylated 28-amino acid peptide that binds to ghrelin receptor. This receptor is responsible for regulating energy consumption, food intake, and growth-hormone release, all of which are important in managing CACS symptoms. Unfortunately, the efficacy of ghrelin to treat CACS is limited because when administered intravenously it has a short half-life of about 30 minutes.³⁵

Anamorelin, a novel selective ghrelin receptor agonist with oral activity and a half-life of about 7 hours, was developed to extend the benefits of stimulating the ghrelin receptor in patients with CACS.³³ Similar to ghrelin, anamorelin has an N-terminal active core that binds to the ghrelin receptor and stimulates neuroendocrine responses that enhance appetite and anabolism, potentially leading to an increase in body weight and lean body muscle mass.^{33,36}

In two ongoing, phase III clinical trials (ROMANA 1 and 2) and a phase III extension trial (ROMANA 3), anamorelin is being tested as treatment for CACS in patients with advanced nonsmall cell lung cancer (NSCLC). Anamorelin is administered at a daily, oral dosage of 100 mg for 12 weeks or until disease progression or unacceptable toxicity.³⁷⁻³⁹ Because positive outcomes observed in patients treated with anamorelin seem to be independent of NSCLC characteristics, clinicians anticipate anamorelin would also have similar results in other cancer types.⁴⁰

Clinical trials: Under the ROMANA program, the safety and efficacy of anamorelin to change lean body mass and muscle strength is being studied over 12 weeks in patients with unresectable stage III or IV NSCLC-related cachexia, who have received, are receiving, or will receive systemic chemotherapy to treat NSCLC.³⁷⁻³⁹ At the 2014 European Society for Medical Oncology Conference, investigators presented joint results from the phase III ROMANA 1 and 2 trials, which compared treatment with anamorelin to placebo in patients with NSCLC-related cachexia. In this randomized trial, investigators reported anamorelin significantly increased lean body mass in both studies compared with placebo. In ROMANA-1, median change in lean body mass was 1.10 kg (95% confidence interval [CI], 0.76 to 1.42) for anamorelin versus -0.44 kg (95% CI, -0.88 to 0.20) for placebo. In ROMANA-2, median change in lean body mass was 0.75 kg (95% CI, 0.51 to 1.00) for anamorelin versus -0.96 kg (95% CI, -1.27 to -0.46) for placebo. However, no statistical difference was reported for hand-grip strength between groups receiving anamorelin or placebo.⁴¹

The most common grade 3–4 anamorelin-related adverse events reported in clinical trials include asthenia, atrial fibrillation, diabetes, dyspnea, hyperglycemia, and nausea.^{33,41} Overall, researchers report that anamorelin is well tolerated with a rate of grade 3 or higher adverse events of 0.9% and 2.7% in the ROMANA 1 and ROMANA 2 trials, respectively.⁴¹ The phase III extension trial, ROMANA 3, will assess long-term safety and tolerability of anamorelin in patients enrolled in the ROMANA 1 and 2 trials who completed treatment and are eligible to receive additional anamorelin.³⁹

Manufacturer and regulatory status: Helsinn Healthcare S.A. (Lugano/Pazzallo, Switzerland) is developing anamorelin for treating CACS. Helsinn Healthcare has reported top-line results from the ROMANA 1 and 2 trials and has begun communications with FDA; however, it intends to wait for the 12-month data from the phase III extension study ROMANA 3 before submitting an application for regulatory approval.⁴⁰ In November 2013, Helsinn Healthcare granted Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan), commercialization rights to distribute anamorelin in Benelux (the economic union of Belgium, the Netherlands, and Luxembourg), France, Germany, Ireland, and the United Kingdom.⁴²

Diffusion and cost: Anamorelin is not yet approved by FDA; therefore, pricing and third-party coverage and reimbursement information is unavailable. However, FDA-approved drugs for treating patients with cancer are typically covered by third-party payers for their FDA-approved indications; therefore, if FDA approves anamorelin for treating patients who have CACS, it is likely that third-party payers would reimburse its use.

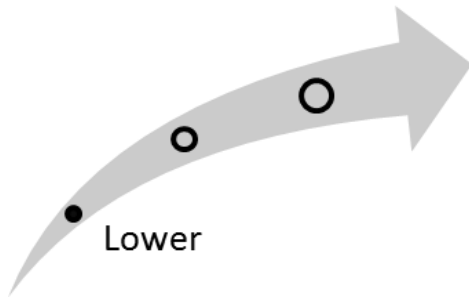
Clinical Pathway at Point of This Intervention

Up to 80% of patients with cancer develop CACS, and researchers believe that it is caused by an onset of hypercatabolism, which evidence suggests is driven by increased serum levels of cytokines, hormones, neuropeptides, neurotransmitters, and tumor-derived factors.⁴³ This increase is caused primarily by the patient's immune cells mounting a response against the tumor or the cancer cells themselves that secrete—in addition to tumor-derived factors—inflammatory cytokines, such as interleukin (IL)-1-beta, IL-6, IL-10, leukemia inhibitory factor, and tumor necrosis factor (TNF)-alpha, which in turn are responsible for augmenting the release of anorexia-inducing hormones 5-HT (serotonin), cholecystokinin, insulin, and leptin.^{43,44} The latter hormones can also travel to the brain, where they induce the release of neurotransmitters and neuropeptides, which can aggravate CACS.⁴³ Because of their ability to block cells from releasing cytokines, megestrol acetate and glucocorticoids have been used as a cachexia treatment to decrease lean muscle deterioration and weight loss, but their efficacy is limited.³⁵ For instance, several clinical trials of megestrol acetate have shown improvement in appetite, food intake, nausea, and weight gain while having tolerable adverse events. However, most of the weight gain comes from adipose tissue and does not significantly improve the survival rate.⁴³ Similarly, corticosteroids also increase appetite, food intake, and weight gain, but the sense of well-being is short lived because of drug-related adverse events, which include insulin resistance, myopathy, water retention, neurological disorders, and skin sensitivity.^{43,44} Additional alternatives include cannabinoids and anti-inflammatory agents (e.g., COX-2 inhibitors, indomethacin, thalidomide) that prevent the synthesis or the activity of cytokines and have shown positive efficacy against cachexia, although further studies are needed to confirm these observations.⁴³

Because most of these interventions have limited activity in treating cachexia, developing novel and effective agents remains challenging. If clinical data on anamorelin continues to show clinical benefit, the drug has the potential to compete with standard CACS treatments.⁴¹ Other treatments in development include antibodies against IL-1-alpha, IL-6, and IL-15, which reportedly increase

hemoglobin levels and prevent loss of lean body mass by blocking the activity of their target cytokines.⁴³⁻⁴⁵ Also, the peptide-nucleic acid immune modulator OHR/AVR118 is also under clinical development; and, its specificity for TNF-alpha and IL-6 reportedly improves appetite, weight, lean body mass, strength, and quality of life.⁴³

Figure 2. Overall high-impact potential: anamorelin for treatment of cancer-related cachexia/anorexia



Although the initial data from the phase III trials are positive and indicate anamorelin has potential to address the unmet need, some experts commenting on this intervention thought the data are too preliminary and short-term (12 weeks) to predict long-term efficacy of anamorelin. They also point out that CACS is caused by a complex mechanism that is not fully understood; therefore, it seems unlikely anamorelin as a monotherapy would be able to alleviate all cachexia symptoms. Besides the potential anamorelin has for treating cachexia, other factors such as patient education and behavior can serve as feedback to help improve quality of life and patient outcomes, one expert indicated. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on anamorelin for treating cancer-related cachexia/anorexia.⁴⁶⁻⁵¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A need exists for novel agents that treat CACS, a syndrome that worsens patient outcomes and increases morbidity, experts agreed unanimously. Standard treatments are not effective and do not improve survival rates, they noted. Because of its novel mechanism to increase anabolism, experts believe anamorelin has a high potential to address a medical need and improve patient outcomes. However, results from the latest clinical trials assessed body mass changes at 12 week follow up, which most experts noted was not long enough to demonstrate that anamorelin will significantly improve CACS over the long term. Even with the lack of long-term data, one clinician considers anamorelin results promising and thinks it has potential to outperform available treatments.⁵⁰

Acceptance and adoption: Data thus far indicate that anamorelin shows some efficacy and is well tolerated; thus, all experts agree both physicians and patients are very likely to adopt it for treating cachexia, especially because it is an oral therapy that is easily self-administered. In contrast, a health devices expert anticipates some patients may choose not to take anamorelin to avoid dealing with drug-related side effects.⁴⁷

Health care delivery infrastructure and patient management: Overall, experts thought adopting anamorelin for treating cancer-related cachexia will not require additional infrastructure and staffing at health centers and will not disrupt patient management. However, patients receiving

anamorelin can develop diabetes; two experts pointed out that if that happens, patient management will be more complex and require closer monitoring.^{47,51}

Health disparities: Experts anticipate the use of anamorelin has a small potential to create health disparities. If approved by FDA, anamorelin would likely be reimbursed by third-party payers, which would make it available to patients regardless of price. However, a research expert indicated that cancer-related cachexia is diagnosed more often in children and the elderly, who are more likely to be underinsured, thus making it difficult for these patients to have access to anamorelin.⁵¹

Colorectal Cancer Intervention

Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

Unmet need: Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States. CRC tends to be slow to develop, and precancerous lesions and early stage CRCs can typically be successfully treated by surgical resection. Successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition; however, the U.S. Centers for Disease Control and Prevention estimated that in 2012, 34.9% of screening-eligible individuals were not up to date with screening recommendations and 27.7% of screening-eligible individuals had never undergone screening.⁵² Therefore, new screening methods are highly desired that could increase the percentage of the population that undergoes recommended CRC screening.

Intervention: Cologuard is an in vitro diagnostic test intended to detect genetic signatures of colorectal precancers and cancers in cells shed from the intestinal walls and excreted with stool.⁵³ To undergo screening, patients provide a stool sample of at least 36 g, which is analyzed for the presence of three markers associated with CRC and precancerous lesions:

- Hypermethylated DNA derived from two genes known to be methylated in CRCs and adenomas (*NDRG4* and *BMP3*)
- Alleles of the *KRAS* gene known to be acquired as somatic mutations in CRCs and adenomas
- Hemoglobin using a highly sensitive fecal immunoassay

Integrating the methylation marker, mutation marker, and hemoglobin results using a logistic-regression algorithm generates a positive or negative result based on cutoffs established by prior analysis of known samples.⁵⁴

The test is ordered by the patient's primary care physician or gastroenterologist. According to the manufacturer, the test kit is shipped directly to the patient who uses it to collect a stool specimen and returns the specimen to Exact Sciences laboratory for processing. Test results are returned to the prescribing physician who in turn relays these results to the patient.⁵⁵

Clinical trials: Cologuard was assessed in a multicenter trial, DEEP-C (n=12,776), comparing the three-component stool DNA test to a commercially available fecal immunochemical test (FIT) alone using colonoscopy as the gold standard. Asymptomatic patients between the ages of 50 and 84 years and considered at average risk of CRC were enrolled in the trial. All patients provided a stool specimen and underwent colonoscopy screening within 90 days of providing the sample. The trial's primary endpoint was the ability of the stool DNA test to detect CRC, with a secondary endpoint of the test's ability to detect advanced precancerous lesions. All stool samples were analyzed in a central laboratory and testers were blinded to results of FIT and clinical findings. Among recruited participants, 9,989 (78.2%) had fully interpretable results, with colonoscopy identifying 65 participants with CRC and 757 participants with advanced precancerous lesions. Compared to FIT, the stool DNA test (including the fecal hemoglobin immunoassay) demonstrated increased sensitivity for CRC (92.3% vs. 73.8%) and precancerous lesions (42.4% vs. 23.8%). Among participants with nonadvanced or negative findings by colonoscopy, the specificity of the stool DNA test and FIT were 86.6% and 94.9%, respectively. In a patient population at average risk for CRC, the number of individuals who would need to be screened to detect one cancer was reported as 154 for colonoscopy, 166 for the stool DNA test, and 208 for FIT.⁵⁶

Manufacturer and regulatory status: Exact Sciences Corp. (Madison, WI) developed the Cologuard stool DNA screening test. In August 2014, FDA approved the Cologuard test as a CRC screening option.⁵⁷ According to the product labeling, the Cologuard test "is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC)

or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.”⁵⁸

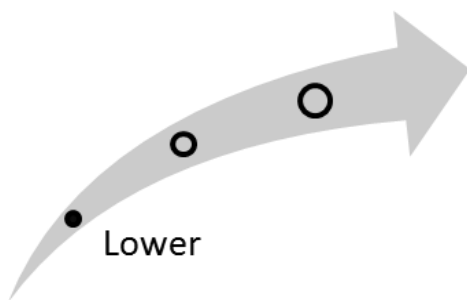
Diffusion and cost: In October 2014, the U.S. Centers for Medicare & Medicaid Services (CMS) used its new parallel review process for the first time to issue a national coverage determination (NCD) for Cologuard (the process enables CMS coverage review at the same time as FDA regulatory approval review, so the decisions come at about the same time). The NCD indicated that Medicare Part B would cover Cologuard use once every 3 years for beneficiaries who are 50–85 years of age, are asymptomatic for CRC, and are at average risk of developing CRC.⁵⁹ Some third-party payers have begun to extend coverage for Cologuard to non-Medicare patients.⁶⁰ These coverage determinations are expected to aid the test’s adoption and diffusion, and Exact Sciences reported that 11,000 Cologuard tests were completed in the first quarter of 2015.⁶⁰

Cologuard’s retail price has been reported as \$600 per test.⁶¹ If used every 3 years, Cologuard would cost approximately \$1,800 per patient over 9 years. For comparison, annual FIT testing costs approximately \$25 per test (\$225 every 9 years) and colonoscopy-based screening costs between \$700 and \$3,000 once every 10 years.⁶²

Clinical Pathway at Point of This Intervention

Several options are available for routine CRC screening in patients with an average risk of developing CRC, including annual fecal occult blood test (FOBT)/FIT, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years.⁶³ For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and biopsy suspicious polyps.⁶³ Multitarget stool DNA testing would provide another CRC screening option that would most likely compete with other noninvasive testing options, such as FOBT/FIT.

Figure 3. Overall high-impact potential: stool DNA molecular test (Cologuard) for colorectal cancer screening



Overall, experts suggested that the large number of screening-eligible patients who are not compliant with screening recommendations and the limited sensitivity of existing noninvasive test methods represent an important unmet need that a novel noninvasive test such as Cologuard could address. However, some commenters questioned the extent to which noncompliant patients would opt for Cologuard-based screening, given the relatively high cost and requirement that patients collect stool samples. Also, expert commenters were divided about the extent to which Cologuard represents an improvement in detection rates relative to stool tests that detect blood. Therefore, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, laboratory, and health systems backgrounds, offered perspectives on this topic.⁶⁴⁻⁶⁹ These comments were received in April 2015, before third-party payers began expanding coverage to non-Medicare beneficiaries. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The experts suggested that available CRC-screening methods have two shortcomings that Cologuard could potentially address: (1) the reluctance or inability of persons eligible for screening to obtain screening and (2) the low sensitivity of noninvasive methods for CRCs/precancers. The majority of expert commenters suggested that this represents an unmet need that is moderately to very important. However, one commenter speaking from a research perspective suggested that Cologuard represents only a small shift relative to available noninvasive tests based on testing for blood in stool.⁶⁹

In this vein, most expert commenters suggested that Cologuard's potential to improve patient health is only minimal, questioning whether Cologuard's availability would actually improve screening rates and raising caveats about the data from the pivotal clinical trial. For example, one research commenter suggested that it seems unlikely that patients compliant with screening via colonoscopy would transition to Cologuard-based screening and that, if Cologuard were used as a replacement for existing fecal blood tests, its impact would be only incremental.⁶⁹ Also, two research experts noted that the pivotal trial of Cologuard involved only a single episode of screening, and questioned whether the observed improvement in sensitivity with Cologuard would be maintained when tests were used iteratively over the course of several years (i.e., Cologuard once every 3 years vs. FIT annually).^{66,68} Conversely, experts viewing Cologuard's potential to improve patient health more favorably suggested that Cologuard's improved sensitivity relative to FIT and potential to increase screening compliance by expanding the menu of testing options represents an important improvement over current screening methods.^{64,67}

Acceptance and adoption: Expert commenters were divided in their opinions about the acceptance and adoption of Cologuard. In terms of factors promoting clinician adoption, expert commenters cited the ease of ordering the test (i.e., no significant training/infrastructure required),⁶⁷ the desire to improve screening rates,⁶⁵ the availability of insurance coverage,⁶⁴ and the need for improved options for patients who refuse colonoscopy.⁶⁶ Conversely, several experts suggested that clinicians would be reluctant to promote Cologuard's adoption, given the availability of other screening options with more established real-world utility. In particular, some experts suggested that clinicians would be highly unlikely to transition patients from colonoscopy to Cologuard. Also, several experts suggested that the substantially higher cost of Cologuard relative to fecal blood tests could dissuade some clinicians and patients from opting for the test. However, it should be noted that experts provided comments before the recent expansion of insurance coverage by some payers to non-Medicare patients, which could limit the impact of this concern. Other factors that experts envisioned as limiting Cologuard adoption included discomfort with collecting stool samples, which could limit compliance with testing in patients prescribed test kits.

Health care delivery infrastructure and patient management: Expert comments on potential changes to health care delivery infrastructure and patient management diverged according to whether the commenter viewed the test as an alternative to colonoscopy or an alternative to other noninvasive test methods. If the multitarget stool DNA test were to replace colonoscopy for some patients, experts suggested, it would cause minimal to moderate shifts in both infrastructure and patient management. They cited the reduction in demand for screening colonoscopy and a shift of required resources away from endoscopy suites. One clinician commenter noted that a shift from outpatient colonoscopy to stool DNA screening would decrease the burden on patients regarding both bowel preparation and the need for transportation assistance after the sedative typically used

during colonoscopies.⁶⁷ On the other hand, if the multitarget stool DNA test were to replace other noninvasive tests, the majority of commenters thought little change would occur in health care infrastructure or patient management, considering that the tests would be used in a highly similar manner to the existing tests (i.e., home sample collection and laboratory analysis). Three experts with research or health systems perspectives suggested that adopting multitarget stool DNA testing among patients who are not compliant with screening recommendations could increase demand for colonoscopy services because of both true-positive and false-positive results.^{64,65,69}

Health Disparities: Experts' opinions differed about the effect of Cologuard on health disparities. Several commenters suggested that a better noninvasive test option could improve screening among underserved patient populations that might not have easy access to colonoscopy, potentially decreasing health disparities. However, one expert suggested that the cost of multitarget stool DNA testing relative to existing noninvasive screening tests could further exacerbate existing health disparities if this cost difference restricts its use.

Fertility After Gonadotoxic Cancer Therapy Intervention

Ovarian Tissue Cryopreservation for Fertility Preservation in Females Undergoing Gonadotoxic Cancer Therapy

Unmet need: Cancer treatments have improved patients' long-term survival; therefore, procedures for maintaining cancer survivors' long-term quality of life are of great interest. Many cancer therapy regimens (i.e., chemotherapy or radiation therapy) are highly toxic to the reproductive system (gonadotoxic) and can permanently impair fertility.^{70,71} Prepubertal girls, adolescents and young adults (AYAs), and older reproductive-age women who require gonadotoxic cancer treatments often express a desire to preserve fertility. AYA cancer centers generally promote discussion of fertility issues between patients and clinicians or counselors. In vitro fertilization (IVF) with subsequent embryo cryopreservation is the only standard option available to AYAs and older women who wish to bear children after cancer remission.⁷² However, IVF is not available to prepubertal girls. Also, this option requires weeks of ovarian stimulation with hormones to mature the follicles/oocytes and, therefore, may be contraindicated for women who must urgently begin treatment or whose cancers may worsen with hormone treatments.⁷³ A new option to preserve fertility involves ovarian tissue cryopreservation and reimplantation of the tissue to the patient after she achieves cancer remission. This option is available to prepubertal girls and reproductive-age women and requires no ovarian stimulation or treatment delay.⁷⁴

Intervention: To perform ovarian tissue cryopreservation, clinicians retrieve a patient's ovarian tissue and cryopreserve it. At a later date, after cancer treatment has been completed, the ovarian tissue can be reimplanted in the patient with the intent of restoring ovarian function and fertility. Surgical techniques and cryopreservation protocols vary among institutions; in this report, we provide a general overview of the process.

Ovarian tissue collection is typically performed as a same-day, outpatient surgical procedure in which the patient is placed under general anesthesia, and the procedure is performed laparoscopically or by laparotomy.⁷² Tissue harvesting can coincide with oophorectomy, and an ovarian biopsy specimen may be sent for histopathologic analysis to rule out the presence of malignant cells.⁷⁵ Typically, the cortex from at least one ovary is sectioned (about 1.0–1.5 mm thick, to capture the primordial follicles) and treated to withstand the freezing process. Tissues are prepared for cryopreservation through slow freezing or vitrification (i.e., rapid cooling). Cryopreservation is often performed at the site of tissue storage and may occur at offsite laboratories of tissue banks.⁷⁶

Once a patient completes treatment, cryopreserved ovarian tissue is reimplanted with the intent of restoring ovarian function and fertility. The ovarian tissue transplant, or autograft, may be placed orthotopically (i.e., in the same, or original, anatomical site) or heterotopically (i.e., at an alternative anatomical location).^{72,76} Orthotopic autotransplantation involves reimplanting the ovarian tissue into the pelvic cavity, either onto the existing ovary or within the uterine environment. When it is medically feasible, this orthotopic placement is preferred and provides a chance of natural pregnancy when the fallopian tubes are intact. If an ovary remains, surgeons will often decorticate this structure to expose the vascular bed and affix the ovarian tissue autograft onto this surface. When both ovaries have been removed, the surgeon may create a peritoneal pouch on the surface of the broad ligament and affix the autograft in place.⁷⁶

As an alternative, surgeons can also place the autograph in a heterotopic location such as the abdominal wall, forearm, or rectus muscle,^{72,75,76} an approach used in patients for whom orthotopic transplantation is not feasible. Reports have demonstrated restored endocrine function with this approach, and mature follicles can be retrieved for in vitro fertilization.⁷⁵⁻⁷⁷

Clinical trials: Several nonrandomized trials are ongoing to examine ovarian tissue cryopreservation in adult females who require gonadotoxic therapies to treat a variety of malignant conditions.⁷⁸⁻⁸³ These trials are assessing the safety and efficacy of ovarian tissue harvesting and reimplantation, successful restoration of ovarian function and hormonal cycling, and the rate of successful pregnancy after reimplantation. Due to the nature of this intervention, large randomized, controlled trials have not been carried out, and collecting outcomes data is a long-term endeavor that depends on when a patient desires pregnancy.

An October 2014 review indicated that 30 live births had been reported worldwide in women who underwent transplantation of autologous cryopreserved ovarian tissue.⁸⁴ The majority of these cases were reported in small series or single case reports.⁸⁵⁻⁹⁰ However, a few centers in Europe have recently reported retrospective analyses of the technique. Imbert and colleagues recently reported a 12-year retrospective analysis of 225 patients who underwent ovarian cryopreservation.⁹¹ Fertility outcomes were available for 114 of these patients of whom 40 (about 35%) experienced premature ovarian failure. Eight of these 40 patients underwent ovarian tissue transplantation, which resulted in three pregnancies. Also, Dolmans and colleagues in March 2013 reported a 15-year retrospective analysis of 476 patients who underwent ovarian tissue cryopreservation for fertility preservation.⁹² Among these patients, 11 patients underwent autotransplantation, resulting in 5 live births and 1 ongoing pregnancy.

In June 2015, Demeestere et al. reported the first case of restored fertility in a patient who had her ovarian tissue cryopreserved before puberty. When the patient was 14 years old, she underwent a hematopoietic stem cell transplantation to treat homozygous sickle-cell anemia. The myeloablative conditioning regimen the patient received to prevent graft-versus-host disease resulted in premature ovarian insufficiency, which is observed in more than 80% of childhood cancer survivors. Ten years after receiving treatment, the patient's cryopreserved ovarian tissue was reimplanted to restore her fertility, which allowed her to conceive and give birth to a healthy baby 2 years after receiving the transplant.⁹³

A major safety concern regarding autologous transplantation of tissue from cancer patients is the potential for transplanted tissue harboring malignant cells to re-seed the patient's cancer. This is a particular concern in patients with hematologic cancers such as leukemia, in which malignant blood cells are disseminated throughout the body.⁹⁴ Recent retrospective studies have detected cancerous cells in only a small minority of ovarian tissue samples taken from patients;^{91,92} however, the potential for cancerous cells to exist below detection limits exists, and research into more intensive detection methods and methods of oocyte maturation that could obviate the need for ovarian tissue transplantation is being pursued.⁹⁴

Manufacturer and regulatory status: A number of medical institutions in the United States offer ovarian tissue cryopreservation.⁹⁵ Several academic medical centers are conducting clinical trials to investigate reimplantation of cryopreserved ovarian tissue for restoring fertility. The following institutions are sponsoring ongoing clinical trials:

- Abramson Cancer Center of the University of Pennsylvania, Philadelphia⁸¹
- Boston IVF, Boston, MA⁸²
- Hadassah Medical Center, Jerusalem, Israel⁷⁸
- Oregon Health & Science University, Portland⁸³
- University of Kansas Medical Center Research Institute, Kansas City⁷⁹
- Weill Medical College of Cornell University, New York, NY⁸⁰

Additionally, the Oncofertility Consortium[®] at Northwestern University (Chicago, IL) is a nationwide network that coordinates fertility preservation research and services for patients with cancer; these services include ovarian tissue cryopreservation and reimplantation.⁹⁶

Diffusion and cost: Adoption of ovarian tissue cryopreservation could be limited by lack of third-party payer coverage. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 5 payers that consider ovarian tissue cryopreservation to be experimental and do not provide coverage (i.e., Anthem, Blue Cross/Blue Shield Massachusetts, CIGNA, Humana, United Healthcare).⁹⁷⁻¹⁰¹ No specific policies were identified for the other six payers.

Although official policies generally do not establish coverage for ovarian tissue cryopreservation, survey results published in 2010 reported that health insurance companies did indeed cover the costs for oncology patients who had undergone these procedures.¹⁰² Such coverage may occur more on a case-by-case basis than under the umbrella of an overall medical coverage policy.

An economic evaluation of fertility preservation treatments published in March 2012 determined that cryopreserving ovarian tissue would cost about \$27,000.¹⁰³ Also, a U.S. fertility clinic published online estimated fees for 2014 that include \$429 for physician consultation, \$445 for blood tests, \$18,000 for the laparoscopic procedure to remove ovarian tissue, \$3,133 for the pathology evaluation, \$1,169 for preparing ovarian tissue, and \$325 for transporting the cryopreserved ovarian tissue to the storage facility. This brings the total cost for the procedure to \$23,501, which would be similar to the economic evaluation estimate once storage costs are included.¹⁰⁴ Additional costs for storing cryopreserved ovarian tissue vary from one private banking facility to another. Some facilities charge an initial fee of \$2,000 to \$4,000 to process the sample plus \$16 to \$38 per month for storage.¹⁰⁵ Other facilities charge yearly fees that range between \$350 and \$425.^{104,106}

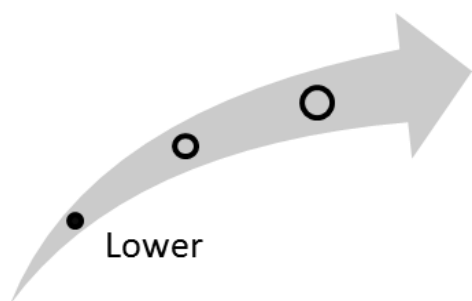
Clinical Pathway at Point of This Intervention

Embryo cryopreservation is the standard of care for fertility preservation in reproductive-age women undergoing gonadotoxic cancer therapy. After hormonal stimulation to mature ovarian follicle(s), mature oocytes are retrieved and the oocytes are then fertilized in vitro. Resulting embryos are cryopreserved until a later date for intrauterine embryo transfer.¹⁰⁷

For patients who require radiation therapy that may affect the ovaries, several techniques exist to minimize damaging radiation exposure. Ovarian transposition is a surgical technique used to reposition the ovaries away from the radiation treatment zone to minimize damage. This technique can alter blood flow to the ovaries, compromising their function, and does not provide protection from chemotherapy effects.^{71,72} Gonadal shields can also be used to minimize radiation exposure to the ovaries, but this technique requires care to ensure that shielding does not prevent adequate radiation dosing to targeted malignant areas.⁷²

Besides ovarian tissue cryopreservation, several investigational approaches exist for fertility preservation: oocyte cryopreservation, oocyte in vitro maturation, and pharmacological ovarian suppression.⁷³ With the exception of gonadal shielding and ovarian transposition to prevent radiation exposure, these fertility preservation options are limited to reproductive-age women.

Figure 4. Overall high-impact potential: ovarian tissue cryopreservation for fertility preservation in females undergoing gonadotoxic cancer therapy



Experts commenting on this topic had divergent opinions, which reflects in part some controversies over views about fertility preservation for female oncology patients and fertility as a therapy overall. Some experts stated that this intervention fills an extremely important unmet need for female cancer patients, while others indicated that fertility preservation is not a critical unmet health care need—but rather a lifestyle choice. Experts commenting on this topic were also divided in their assessment of the likelihood of adoption. While some commenters suggested that patients and clinicians would likely opt for a technique that could increase the likelihood of fertility, other commenters suggested that the limited available data on the procedure and the potential for reintroducing cancer through ovarian tissue transplantation could limit adoption. Based on these mixed views on the part of experts commenting, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on ovarian tissue cryopreservation in women undergoing gonadotoxic cancer therapy.¹⁰⁸⁻¹¹³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts' opinions diverged on the significance of the unmet need of fertility preservation in females undergoing gonadotoxic cancer treatments. One expert speaking from a clinical perspective cited increasing awareness about the importance of fertility preservation in younger women in whom cancer has been diagnosed and suggested that additional fertility preservation methods such as ovarian tissue cryopreservation represents a very important complement to existing methods.¹⁰⁹ Conversely, one research expert indicated that the magnitude of the unmet need potentially addressed by ovarian tissue cryopreservation was of little importance, suggesting that only a small number of prepubertal patients would be served by adding ovarian tissue cryopreservation to existing methods.¹¹³ Other commenters viewed the unmet need as being of minimal to moderate importance. These commenters uniformly suggested that ovarian tissue cryopreservation has the potential to restore fertility in females who experience premature ovarian failure due to gonadotoxic chemotherapy; however, several commenters questioned whether loss of child-bearing potential represents a significant unmet medical need relative to other health care needs.

These experts were similarly divided on the potential of ovarian tissue cryopreservation to improve patient health. One clinical expert indicated that the procedure has a large potential to improve patient health, suggesting that loss of fertility is a significant quality-of-life issue and that the potential of ovarian tissue cryopreservation to restore fertility for some patients would be greatly beneficial.¹⁰⁹ Conversely, one research expert suggested that ovarian tissue cryopreservation has no potential to change or improve patient health outcomes.¹¹³ Experts viewing the procedure as having

minimal to moderate potential to improve patient health cited the increasing number of viable pregnancies reported from patients who have undergone the procedure. However, these commenters also noted that the number of successful pregnancies is still small, that potential long-term consequences for offspring generated through this method have not had time to emerge, and that more data are needed regarding the safety of the procedure as it relates to the potential reintroduction of malignant cells.

Acceptance and adoption: Experts were also divided in their opinions regarding the likelihood of clinician acceptance and adoption. Commenters who thought that moderate to wide adoption is likely suggested that ovarian tissue cryopreservation offers the potential of improved patient quality of life. They stated that the surgical procedure and cryopreservation protocols are both familiar to and accessible for physicians to use. Commenters who thought clinicians would be unlikely to adopt cited the small amount of safety and efficacy data available and suggested that clinicians may be more focused on treating the cancer than on longer-term quality-of-life issues or concerns regarding the potential for reintroducing cancer.

However, the majority of commenters thought that moderate to wide adoption by patients would be likely, citing the relatively low risks involved in the ovarian tissue collection procedure and patient desire for options to preserve fertility. However, several experts noted that the procedure's cost and potential lack of reimbursement by insurers could limit access and adoption. Additional barriers to adoption envisioned by commenters included the small amount of data available on the procedure to date and the potential for parents of younger children with cancer to be uncomfortable making decisions regarding their child's future fertility.^{110,112}

Health care delivery infrastructure and patient management: Little to no disruption in health care delivery infrastructure and patient management was envisioned by the experts commenting. They indicated that the technology and infrastructure to perform these procedures are readily available. Similarly, the majority of experts commenting did not envision significant changes in patient management, suggesting that ovarian tissue cryopreservation simply represents another option to cryopreserving embryos or oocytes. Small disruption to the care pathway was seen by multiple commenters, because of the invasive nature of the procedure and the need to coordinate cancer treatment with a fertility preservation regimen. However, one clinical expert suggested that ovarian cryopreservation would provide an option for patients unable to undergo cryopreservation of embryos or oocytes and, therefore, would represent a large shift in patient management for these patients.¹⁰⁹

Health disparities: Because of the procedure costs and likelihood that few health plans would provide coverage, experts concurred that this option would likely be available only to economically advantaged patients. This may further increase health disparities for women and families affected by cancer who cannot afford fertility preservation.

Gastric Cancer Intervention

Ramucirumab (Cyramza) for Treatment of Gastric Cancer

Unmet need: The majority of patients with gastric cancer present with locally advanced or metastatic disease.¹¹⁴ Despite recent advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for these patients remains poor.¹¹⁵ Inhibiting the vascular and epidermal growth factor pathways using targeted drugs has been a focus of experimental therapies for treating gastric cancers, but to date, these therapies have had limited success.^{114,116,117} Ramucirumab (Cyramza®) is a novel, targeted approach to inhibiting angiogenesis (i.e., formation of new blood vessels) via direct interaction with vascular endothelial growth factor receptor 2 (VEGFR2). Through its novel approach to inhibiting angiogenesis, ramucirumab may improve clinical outcomes in patients with advanced gastric cancers.

Intervention: Vascular endothelial growth factors (VEGFs) are highly expressed by many tumor types and are thought to signal to their cognate receptors (e.g., VEGFR2) on endothelial cells, promoting these cells' proliferation, migration, and survival. These processes are essential to blood vessel development (angiogenesis), which is thought to be required for both the growth of large tumors and metastasis (i.e., systemic spread) of cancers. Increased VEGF expression in tumors and serum is linked with lymph node involvement, metastasis, and poor outcomes for patients with advanced gastric cancer, providing a rationale for this approach.^{114,118-120}

Existing angiogenesis inhibitors using the VEGF/VEGFR signaling axis target either a single VEGFR ligand (e.g., VEGF-A by bevacizumab) or inhibit multiple receptor tyrosine kinases (e.g., the multikinase inhibitors sorafenib and sunitinib). Because several VEGFs exist in the body, targeting a single VEGF may allow residual VEGFR activation by other ligands. Conversely, because available small-molecule kinase inhibitors simultaneously modulate several signaling pathways, they may have less favorable efficacy or toxicity profiles than agents of greater specificity.

Ramucirumab is a human monoclonal antibody specific for VEGFR2. Ramucirumab binds to the extracellular domain of VEGFR2, blocking this receptor from interacting with any VEGF ligands and inhibiting the downstream signaling cascade.^{121,122} By targeting VEGFR2 and preventing interaction with all VEGFR2 ligands, ramucirumab may exhibit enhanced target inhibition and higher specificity than available VEGF/VEGFR-targeted agents.¹²² Among VEGFR2-specific agents, ramucirumab is furthest along in development.¹²¹ It is administered intravenously at a dosage of 8 mg/kg every 2 weeks of a 4-week cycle.¹²³

Clinical trials: Ramucirumab has been tested as second-line monotherapy for gastric cancer (REGARD trial)¹²⁴ and as combination therapy with paclitaxel (RAINBOW trial).^{125,126} Also, ramucirumab is also being tested in the first-line setting in combination with cisplatin and capecitabine as treatment for patients with gastric cancer whose disease has progressed after adjuvant or neoadjuvant systemic therapy (RAINFALL trial).¹²⁷

Results from a phase III, randomized, double-blind, placebo-controlled trial of 355 patients (REGARD) were published in January 2014.¹²⁴ Used as a second-line monotherapy at a dosage of 8 mg/kg every 2 weeks, ramucirumab met its primary endpoint of improving overall survival in patients (5.2 months with ramucirumab vs. 3.8 months with placebo; HR, 0.776; p=0.042).¹²⁴

Although the overall survival improvement in the REGARD trial seems incremental, these results have similar survival benefits to those observed in trials comparing second-line cytotoxic chemotherapy to best supportive care. The results from this trial confirm the participation of VEGFR2 in advanced gastric cancer and the importance of targeting this pathway to improve outcomes in this patient population.¹²⁴ As monotherapy, ramucirumab treatment was well tolerated by patients. The drug's prescribing information lists the most common side effects observed in

patients with advanced gastric cancer: hypertension and diarrhea.¹²³ In the REGARD trial, the most common grade 3 adverse events experienced by patients were as follows:^{123,124}

- Hypertension (8% ramucirumab vs. 3% placebo)
- Fatigue (6% vs. 10%)
- Anemia (6% vs. 8%)
- Abdominal pain (6% vs. 3%)
- Ascites (4.2% vs. 4.3%)
- Hyponatremia (3.4% vs. 0.9%)
- Decreased appetite (3% vs. 3%)

As a combination therapy, ramucirumab and paclitaxel treatment reportedly met the endpoint of increasing overall survival by 2.27 months (9.63 months with ramucirumab plus paclitaxel vs. 7.36 months with paclitaxel; HR, 0.807; $p=0.0169$).^{125,126}

Researchers presented the results from a phase III, randomized, double-blind, placebo-controlled trial of 665 patients (RAINBOW) at the 2014 Gastrointestinal Cancers Symposium. Even though median overall survival was 1.6 times higher in the ramucirumab and paclitaxel combination group than in the ramucirumab-alone group, drug-related toxicities occurred at least twice as often in the combination-therapy group. The most common grade 3 and higher adverse events reported in the RAINBOW trial were as follows:¹²⁵

- Neutropenia (40.7% combination vs. 18.8% paclitaxel)
- Leukopenia (17.4% vs. 6.7%)
- Hypertension (14.1% vs. 2.4%)
- Anemia (9.2% vs. 10.3%)
- Fatigue (7.0% vs. 4.0%)
- Abdominal pain (5.5% vs. 3.3%)
- Asthenia (5.5% vs. 3.3%)

Manufacturer and regulatory status: Ramucirumab was developed by ImClone Systems, a subsidiary of Eli Lilly and Co. (Indianapolis, IN). Based on the REGARD trial results, Lilly submitted a biologics license application (BLA) to FDA for ramucirumab monotherapy for gastric cancer; FDA granted the BLA priority review. It approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, after fluoropyrimidine/platinum-based chemotherapy.¹²⁸ In November 2014, on the basis of results from the RAINBOW trial, ramucirumab received a second FDA approval as second-line treatment in combination with paclitaxel for advanced gastric cancer.¹²⁹ In December 2014, on the basis of the phase III REVEL trial data, FDA approved ramucirumab in combination with docetaxel for treating metastatic nonsmall cell lung cancer (NSCLC) that has progressed after platinum-based chemotherapy. This indication is also intended as treatment for NSCLC caused by genetic alterations in either epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) and that has progressed after targeted therapy.¹³⁰ In April 2015, on the basis of phase III RAISE trial data, FDA approved second-line use of ramucirumab in combination with FOLFIRI for treating patients with metastatic CRC that has progressed after bevacizumab-, oxaliplatin-, and fluoropyrimidine-based chemotherapy.^{131,132}

Diffusion and cost: Ramucirumab costs about \$6,300 for six vials of 100 mg/10 mL according to a query of the GoodRx database in May 2015.¹³³ The recommended dosing for a typical patient weighing 70 kg is 560 mg (8 mg/kg) per infusion, which is given once every 2 weeks and would cost about \$12,000 for each month of treatment.¹³³⁻¹³⁵ For patients who are uninsured or underinsured who are prescribed an oncology product of Lilly, the Lilly PatientOne program offers reimbursement assistance to eligible patients.¹³⁶

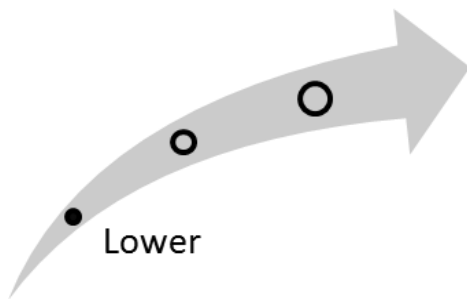
A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 6 payers with policies covering ramucirumab as medically necessary when prescribed according to FDA-approved indications.¹³⁷⁻¹⁴² As an IV medication administered in the health care setting, ramucirumab may be covered under Medicare Part B benefits. CMS has assigned an HCPCS Level II code (i.e., C9025) to describe the injection of 5 mg of ramucirumab; this code may be reported several times to describe the administered dose of the drug.¹⁴³

Clinical Pathway at Point of This Intervention

Metastatic gastric cancer is typically treated with systemic chemotherapy.^{117,144} In cases of acute bleeding or gastrointestinal blockage, radiation therapy and/or surgical resection may be employed. First-line chemotherapy typically includes a combination of fluoropyrimidine/platinum-based drugs with or without targeted molecular therapy (e.g., the monoclonal antibody trastuzumab in the case of human epidermal growth factor receptor 2 [EGFR2]-positive disease).^{115,117,120} Additional targeted therapies under investigation for treating gastric cancer act on a variety of molecular signaling pathways, including EGFR, hepatocyte growth factor receptor (cMET), mTOR, and VEGF.^{119,120}

In clinical trials for gastric cancer, ramucirumab is administered in combination with paclitaxel or best supportive care as second-line treatment and is likely to be part of combination therapy for metastatic disease that includes other systemic chemotherapies, targeted therapies, or both.¹⁴⁵

Figure 5. Overall high-impact potential: ramucirumab (Cyramza) for treatment of gastric cancer



Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer because limited options are available. Although ramucirumab showed efficacy in patients with gastric cancer, some experts thought it has limited potential to fulfill this need because survival was marginally increased and the benefits might not outweigh the increase in adverse events. However, other experts anticipate as research continues, different treatment combinations that include ramucirumab could potentially have survival benefits longer than those reported in the latest clinical trials. Most experts commenting on ramucirumab agreed that a need exists for new therapies for advanced gastric cancer. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of ramucirumab for treating gastric cancer.¹⁴⁶⁻¹⁵¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Even with advances in surgery, radiation therapy, and chemotherapy, outcomes for patients with gastric cancer are very poor. The experts agreed that an unmet need exists for targeted therapies and that ramucirumab has potential to address this need. However, the experts were concerned about the severe adverse events reported with ramucirumab and chemotherapy as second-line treatment. Three experts pointed out that survival increased by only a few months.^{147,150,151} In contrast, a clinician stated the lack of treatment options would lead patients to tolerate the side effects if it meant extending their lives.¹⁵¹

Acceptance and adoption: Experts anticipate that both physicians and patients will adopt ramucirumab for treating gastric cancer, because of limited second-line alternatives. They thought it would most likely be adopted as combination therapy. Despite the cost and adverse events, two clinicians anticipate patients will probably accept ramucirumab because it would be the only alternative with potential to extend overall survival.^{150,151} However, an expert remarked that some patients might not consider the potential of an overall survival extension of a couple of months to be worth the added side effects of ramucirumab.¹⁴⁷

Health care delivery infrastructure and patient management: As an intravenously administered drug, ramucirumab is not expected to change health care delivery and infrastructure and would be easily integrated into clinical care at cancer centers and infusion clinics, noted experts. Patient management is also expected to remain unaffected. However, one expert anticipated treatment pattern shifts from irinotecan-based therapies to taxane-ramucirumab doublets.¹⁵⁰

Health disparities: Three experts thought that the high cost of ramucirumab could increase disparities, especially for patients with low socioeconomic status who are uninsured or underinsured with high co-pays.^{146,148,150} However, an expert pointed out that third-party payers cover use of ramucirumab for gastric cancer; thus, it would not affect disparities.¹⁴⁹ Even if most expenses are covered by insurance, a clinician stated, ramucirumab is an added cost because about 75% of patients who require second-line treatment receive combination therapy.¹⁵⁰

Hematologic Malignancy Interventions

Blinatumomab (Blincyto) for Treatment of Acute Lymphoblastic Leukemia

Unmet need: Acute lymphoblastic leukemia (ALL) is a heterogeneous collection of aggressive hematologic malignancies arising from cells of the lymphoid lineage. For adult patients in whom ALL has been diagnosed, cure rates using standard treatments are only about 20% to 40%, and survival of patients with recurrent or refractory ALL is only 4.5–6.0 months.¹⁵² Therefore, substantial interest exists in novel approaches to treating patients with ALL.

Intervention: Blinatumomab (Blincyto®) is the first in a new class of immunotherapy drugs known as bi-specific T-cell engagers (BITEs) to come to market.¹⁵³ BITEs are chimeric antibody constructs that contain binding domains for both a target cell-specific antigen and an immune cell-specific antigen. By binding both antigens simultaneously, the BITE construct purportedly brings the T cells into close proximity with cancer cells, potentially promoting destruction of diseased cells by the T cell. In the case of blinatumomab, the target cell-specific antigen is CD19, a protein expressed by cells of the B-cell lineage, and the immune cell-specific antigen is CD3, a component of the T-cell receptor complex expressed by mature T cells. CD19 is expressed only by the ALL subtype arising from the B-cell lineage; therefore, only this form of ALL is eligible for blinatumomab treatment.¹⁵⁴

In the bloodstream, blinatumomab has a short half-life; therefore, the drug is given by continuous IV infusion. Patients typically receive blinatumomab in 6-week cycles consisting of 4 weeks of continuous infusion followed by 2 weeks off treatment. After a loading dose of 9 mcg per day for week 1 of the first treatment cycle, patients receive blinatumomab at a dose of 28 mcg/day.¹⁵⁴

Clinical trials: The main trial supporting FDA approval of blinatumomab was an open-label, single-arm study with a primary endpoint of the rate of complete response (CR) or complete response with partial hematologic recovery (CRh) within first two treatment cycles.¹⁵⁵ In this trial, 185 adult patients with recurrent/refractory ALL received blinatumomab treatment, and the primary endpoint was met in 43% of these patients (33% CR and 10% CRh). The most common adverse reactions reported in patients treated with the drug were pyrexia (fever), headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation.¹⁵⁴ Additionally, the prescribing information includes a black box warning regarding the potential for two potentially life-threatening adverse events: cytokine release syndrome and neurological toxicities, which occurred in 2% and 11% of patients, respectively.^{154,155} These severe adverse events typically occurred within the first week of blinatumomab administration; the prescribing information recommends that patients be hospitalized for the first 9 days of treatment cycle 1 and the first 2 days of treatment cycle 2.¹⁵⁴

Manufacturer and regulatory status: Blinatumomab was developed by Amgen, Inc. (Thousand Oaks, CA). In December 2014, FDA approved blinatumomab under the agency's accelerated approval pathway for treating Philadelphia chromosome-negative, recurrent or refractory B-cell precursor ALL.¹⁵³ Blinatumomab's biologic license application had been granted priority review by the agency, and the accelerated approval came 5 months ahead of the Prescription Drug User Fee Act-specified decision date.¹⁵³ Before the approval, FDA had granted blinatumomab orphan drug and breakthrough therapy designations.^{156,157} The accelerated approval requires that the potential clinical benefit of blinatumomab be confirmed in a larger trial, and a confirmatory phase III trial (the TOWER trial) is ongoing.¹⁵⁸ Also, FDA required that a Risk Evaluation and Mitigation Strategy (REMS) program be instituted for blinatumomab to inform

health care workers of the potential for severe adverse events (i.e., cytokine release syndrome and neurological toxicities).¹⁵⁹

Diffusion and cost: In December 2014, Amgen announced that blinatumomab would be priced at \$89,000 per 4-week cycle.¹⁶⁰ In the phase II trial supporting FDA approval in the recurrent/refractory setting, patients received a median of two treatment cycles (range 1–5).¹⁵⁴ Therefore, drug costs associated with a typical patient receiving blinatumomab would be approximately \$178,000. Additional costs associated with blinatumomab treatment would include administration costs associated with the 24-hour continuous infusion and costs for hospital stays during the first days of treatment cycles 1 and 2.¹⁵⁴

Our searches of representative, private, third-party payers that publish their coverage policies online identified 4 policies (Horizon Blue Cross Blue Shield NJ, Blue Cross Blue Shield of Tennessee, HealthPartners, Regence) for blinatumomab, which indicated that blinatumomab was covered for its FDA-approved indication.¹⁶¹⁻¹⁶⁴

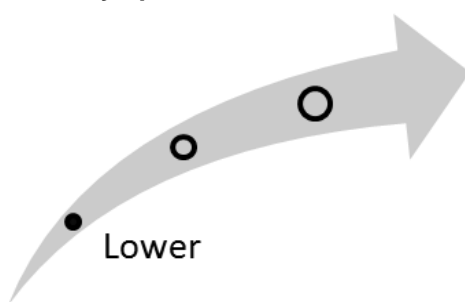
Clinical Pathway at Point of This Intervention

Treatment of patients who have ALL is highly personalized and varies with features of the patient's disease, patient age and any comorbidities, goals of therapy, duration of any prior remission, and type of any previous ALL treatment. In broad terms, an episode of ALL treatment consists of a series of treatments referred to as follows:

- Induction, intended to induce a remission (i.e., deplete leukemic cells and restore normal hematopoiesis)
- Consolidation/intensification, to eliminate any remaining leukemic cells
- Maintenance, to prevent disease recurrence

In the recurrent/refractory setting, no standard of care exists;¹⁶⁵ however, patients with Philadelphia chromosome–negative, B-cell ALL may undergo induction therapy with multidrug regimens such as augmented hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), clofarabine-containing regimens, cytarabine-containing regimens, or alkylator combination regimens. Alternatively, patients may undergo monotherapy with vincristine sulfate liposome injection.¹⁵² For adult patients with recurrent/refractory disease, allogeneic stem cell transplant is the only treatment that has demonstrated the potential to induce long-term remissions and, therefore, patients whose disease responds to induction therapy may be bridged to stem cell transplant in the consolidation/intensification phase of treatment.¹⁶⁵ The recent FDA approval of blinatumomab provides another induction treatment option for patients with recurrent/refractory ALL.

Figure 6. Overall high-impact potential: blinatumomab (Blinicyto) for treatment of acute lymphoblastic leukemia



Expert comments indicated that available treatments for ALL have significant shortcomings, representing a substantial unmet need. Also, given this need for novel treatments and the promising

responses seen in initial trials of blinatumomab, expert comments indicated that blinatumomab is likely to be adopted widely by both patients and physicians alike. However, experts also cautioned that randomized controlled trials of blinatumomab would be needed to confirm the potential clinical benefit. Also, as a drug likely to be given in a standard ALL treatment setting to a small number of patients, blinatumomab was not seen by expert commenters as causing significant shifts in health care infrastructure or patient management. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.¹⁶⁶⁻¹⁷¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for more effective treatments in adult patients with recurrent/refractory ALL was seen as substantial by the majority of expert commenters, citing the poor prognosis of patients with available treatment options. Expert commenters suggested a substantial unmet need and also noted the lack of noncytotoxic chemotherapies in this patient population, and suggested that the immune-based mechanism of action offers a potentially important alternative. However, multiple commenters also noted that the magnitude of the unmet need blinatumomab could address is limited by the small number of adult patients in whom B-cell precursor, Philadelphia chromosome–negative ALL is diagnosed each year.

Blinatumomab's potential to improve patient health was also viewed favorably by the majority of expert commenters, who cited the promising response rates observed in completed single-arm studies. Two clinical commenters also thought the available data suggested that blinatumomab improved patient survival relative to historical controls.^{170,171} However, several commenters also noted that the results observed in single-arm trials of blinatumomab need to be confirmed in randomized trials. Additionally, several commenters noted the significant toxicity associated with blinatumomab treatment. One such researcher who commented suggested that the high rate of adverse events leaves blinatumomab with only minimal potential to improve patient health.¹⁶⁸ A clinical commenter suggested that the rates and consequences of these adverse events would need to be carefully monitored in larger studies.¹⁷⁰

Acceptance and adoption: Blinatumomab is likely to be moderately to widely adopted by both patients and physicians according to the majority of commenters. Factors driving acceptance mentioned by several commenters included the limited treatment options for adults with ALL and the promising response rates observed in single-arm trials of blinatumomab. Also, two clinical commenters suggested that the ease with which blinatumomab could be incorporated into treatment protocols would promote its adoption.^{170,171} Although the majority of commenters suggested that blinatumomab adoption would be strong, several reviewers cautioned that the high rate and serious nature of some adverse events could dissuade some clinicians and patients from adopting the drug. One expert with a clinical perspective suggested that this would require careful patient selection for blinatumomab treatment.¹⁷⁰ One commenter with a research perspective suggested that the high rate of adverse events would lead to only minimal uptake of the drug by clinicians and patients.¹⁶⁸

Health care delivery infrastructure and patient management: Blinatumomab would have only modest effects on health care delivery infrastructure and patient management, according to the expert commenters. Potentially burdensome aspects of blinatumomab's administration include the requirement for hospitalization during the first days of treatment and the need to monitor patients for severe adverse events as listed in the REMS. However, commenters suggested that these represent small shifts because of the familiarity of clinicians who would use blinatumomab with

treating acutely ill leukemia patients with aggressive drug regimens and because of the relatively small number of patients who would be expected to receive blinatumomab treatment.

Health disparities: Blinatumomab has little to no potential to address health disparities according to expert commenters. However, several commenters noted that the high cost of the treatment could widen any existing disparities based on socioeconomic means or access to health insurance.

Ibrutinib (Imbruvica) and Idelalisib (Zydelig) for Treatment of Non-Hodgkin's Lymphomas

Unmet need: Non-Hodgkin's lymphoma (NHL) comprises a set of malignancies that arise from lymphocytes of the immune system. NHLs can derive from either B cells or T cells; however, the majority are of B-cell origin. Treatment of B-cell NHLs has improved in recent years by optimizing chemotherapy regimens and introducing the CD20 antibody rituximab. However, many patients with NHL experience disease recurrence, particularly patients with certain NHL subtypes such as chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. For patients with these conditions whose disease has recurred and resists rituximab, few treatment options exist. Moreover, patients with some forms of CLL, such as CLL harboring a deletion on the short arm of chromosome 17, have a poor prognosis.

Intervention: Ibrutinib (Imbruvica®) is a first-in-class, orally administered, small molecule drug that inhibits Bruton's tyrosine kinase (Btk), a nonreceptor tyrosine kinase that plays several roles in regulating B lymphocytes. Proliferation and survival of malignant B cells may be driven by chronic signaling through the B-cell receptor pathway, which activates several molecular pathways regulating these processes (e.g., Akt, extracellular signal-regulated kinase, NF-κB). Btk is essential for the B-cell receptor-mediated activation of these pathways; therefore, inhibiting Btk may inactivate these pathways, potentially depriving malignant B cells of signals driving proliferation and survival.¹⁷² Besides Btk's role in regulating proliferation and survival downstream of the B-cell receptor, it may also play a role in regulating the trafficking and retention of malignant B cells in the lymph nodes. Lymph nodes may represent privileged sites within the body that play a role in the pathogenesis of B-cell malignancies. Btk has been shown to regulate both integrin-mediated adhesion downstream of the B-cell receptor and chemokine-mediated trafficking downstream of various chemokine receptors. Inhibiting Btk with ibrutinib results in an egress of malignant B cells from the lymph nodes into the peripheral blood, which is thought to be caused by inhibiting these pathways.^{173,174}

Idelalisib (Zydelig®) is a first-in-class, orally administered, small-molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta.^{175,176} PI3K plays a central role in regulating fundamental processes such as cell growth, proliferation, and survival. In certain cancers, including NHLs, the PI3K pathway becomes highly active and is thought to contribute to malignant transformation. Like Btk, PI3K signals downstream of the B-cell receptor, and it has been hypothesized to play a role in malignant transformation caused by chronic B-cell receptor signaling.¹⁷² Four PI3K catalytic subunit isoforms exist: alpha, beta, gamma, and delta. The delta isoform is predominantly expressed in immune-system cells, particularly leukocytes, and is thought to play a role in regulating leukocyte proliferation. Idelalisib is selective for the PI3K delta isoform; therefore, its PI3K pathway-inhibiting activity may be limited to hematologic cells, potentially targeting malignant B cells while limiting systemic toxicity that might be associated with pan-PI3K inhibition.^{177,178}

Clinical trials: Investigators have reported results from several trials of ibrutinib and idelalisib for treating various NHLs.

From a single-arm, open-label trial (n=85) of ibrutinib (420 or 840 mg, once daily) in patients with CLL who had undergone at least two treatments, Byrd and colleagues (2013) reported an overall response rate (as defined by the International Workshop on Chronic Lymphocytic Leukemia [IWCLL] criteria) of 71%. As noted above, ibrutinib's mechanism of action may lead to egress of B cells from the lymph nodes, leading to an increase in absolute lymphocyte count (i.e., lymphocytosis) in a substantial subset of patients. An additional 18% of patients met all IWCLL criteria for partial response except for the absolute lymphocyte count.¹⁷⁹

In a separate single-arm, open-label trial of ibrutinib (420 mg, once daily) in 53 patients with high-risk CLL (risk factors: 17p deletion [n=29], aged 65 years or older [n=24]), Farooqui and colleagues reported an overall response rate of 66%, with an additional 28% of patients exhibiting partial response with lymphocytosis.¹⁸⁰ Importantly, both ibrutinib trials in patients with CLL demonstrated equivalent response rates in patients with or without a 17p deletion.^{179,180}

More recently, researchers presented results from the RESONATE and HELIOS randomized controlled trials of ibrutinib in patients with CLL. The open-label RESONATE trial enrolled two groups of patients who were poor candidates for purine analog therapy: (1) patients with either CLL or small lymphocytic lymphoma who had a short duration of response to chemoimmunotherapy and (2) patients with coexisting illnesses, an age of 70 years or more, or a chromosome 17p deletion. Patients (n=391) were randomly assigned to treatment with either ibrutinib (420 mg, once daily) or ofatumumab (300 mg initial dose, 2,000 mg weekly for weeks 2–8, and 2,000 mg every 4 weeks for weeks 12–24). Compared with patients receiving ofatumumab, patients receiving ibrutinib exhibited improved progression-free survival (median not reached vs. 8.1 months; HR, 0.215; p<0.0001) and improved overall survival (median not reached in either arm; HR, 0.434; p=0.005).¹⁸¹ Investigators noted that the progression-free survival benefit observed for ibrutinib was maintained in the subgroup of patients with a chromosome 17p deletion (median not reached vs. 5.8 months; HR, 0.25; 95% CI, 0.14 to 0.45).¹⁸²

The double-blind HELIOS trial enrolled patients with recurrent/refractory CLL or small lymphocytic leukemia who had undergone at least one chemotherapy regimen. Patients were randomly assigned to receive either standard therapy consisting of bendamustine and rituximab (BR) plus placebo or BR plus ibrutinib (420 mg once daily). Compared with patients receiving BR plus placebo, patients receiving BR plus ibrutinib demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (median not reached vs. 13.3 months, HR=0.0203; 95% CI, 0.150 to 0.276; p<0.0001). This progression-free survival result was obtained at an interim analysis (median followup 17.2 months); because of the observed results, the trial was unblinded and patients in the BR plus placebo arm with confirmed progressive disease were allowed to cross over to ibrutinib treatment.¹⁸³

For patients with mantle cell lymphoma, data from a single-arm, open-label trial of ibrutinib (560 mg, once daily) in 111 patients with recurrent or refractory disease, Wang and colleagues reported an overall response rate of 68% (21% complete response, 47% partial response).¹⁸⁴

For patients with Waldenström's macroglobulinemia, data are available from a single-arm, open-label trial of ibrutinib monotherapy (420 mg, once daily) in 63 patients who had received at least one prior treatment. Treon and colleagues reported an overall response rate of 90.5% (including a major response rate of 73%). Also, investigators reported rates of progression-free and overall survival at 2 years of 69.1% and 95.2%, respectively.¹⁸⁵

In clinical trials, ibrutinib was reported as being well tolerated, with the majority of adverse events being of mild-to-moderate severity.^{179,180,182,185} Additionally, data from the HELIOS trial combining ibrutinib with bendamustine and rituximab reported an adverse profile consistent with the known toxicity of the individual drugs.¹⁸³ According to ibrutinib's prescribing information, common adverse events reported in patients taking ibrutinib included thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory tract infection, and rash. Also, the prescribing information contains warnings and precautions regarding the potential for hemorrhage, infections, atrial fibrillation, second primary malignancies, tumor lysis syndrome in patients with high tumor burden, and embryo-fetal toxicity.¹⁸⁶

Regarding idelalisib, investigators published results in 2014 from a randomized, double-blind, placebo-controlled trial of patients with recurrent/refractory CLL.¹⁸⁷ In this trial, 220 patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses

received rituximab and either idelalisib (150 mg twice daily) or matching placebo. On the primary endpoint of progression-free survival, the median progression-free survival had not been reached at the time of analysis in the idelalisib group; a median progression-free survival of 5.5 months was reported in the placebo group (HR for progression or death, 0.15; $p < 0.001$). Overall response rate also favored patients in the idelalisib arm compared with response rate in patients in the placebo arm (81% vs. 13%; odds ratio, 29.92; $p < 0.001$). Serious adverse events occurred in 40% of patients in the idelalisib arm compared with 35% of patients in the placebo arm.

More recently, investigators presented results from a second randomized controlled trial in patients with recurrent CLL.¹⁸⁸ In this trial, 261 patients with recurrent CLL were randomly assigned in a 2:1 ratio to receive either idelalisib (150 mg twice daily) plus ofatumumab or placebo plus ofatumumab. The combination of idelalisib plus ofatumumab demonstrated a significant improvement in the primary endpoint of progression-free survival compared with such survival under ofatumumab alone (16.3 vs. 8.0 months; HR, 0.27; $p < 0.0001$). The overall response rate also favored the combination arm (75.3% vs. 18.4%; odds ratio, 15.9; $p < 0.0001$). Investigators reported that toxicity of the idelalisib-containing regimen was manageable and similar in profile to previous reports.

Investigators also published results from a trial of idelalisib in patients with recurrent/refractory indolent NHL (follicular lymphoma, small lymphocytic lymphoma, marginal-zone lymphoma, or lymphoplasmacytic lymphoma) who had received between 2 and 12 previous indolent NHL therapies (median 4).¹⁸⁹ In this trial ($n = 125$), all patients received idelalisib (150 mg twice daily). Investigators reported a 57% response rate, including a 6% complete response rate.

In clinical trials, treatment with idelalisib was reported as being well tolerated, with the majority of adverse events being mild to moderate in severity.^{187,189} Frequent adverse events associated with idelalisib monotherapy included cough, diarrhea, dyspnea, fatigue, pneumonia, fever, and rash.¹⁸⁹ Frequent adverse events associated with idelalisib used in combination with rituximab included chills, cough, fatigue, infusion-related reactions (due to rituximab infusion), nausea, and fever. Rates of chills, diarrhea, fever, and rash were higher in the idelalisib plus rituximab arm than in the placebo plus rituximab arm.¹⁸⁷ Idelalisib's prescribing information carries a black box warning regarding the potential for the following fatal and/or serious toxicities: hepatotoxicity, diarrhea or colitis, pneumonitis, and intestinal perforation.¹⁹⁰

Manufacturer and regulatory status: Ibrutinib was developed by Pharmacyclics, Inc. (Sunnyvale, CA), in collaboration with the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). In May 2015, AbbVie (North Chicago, IL) acquired Pharmacyclics, which will be a wholly owned subsidiary of AbbVie.¹⁹¹ FDA granted ibrutinib breakthrough therapy status for three indications: (1) CLL harboring a 17p deletion, (2) recurrent/refractory mantle cell lymphoma, and (3) Waldenström's macroglobulinemia.¹⁹² In November 2013, FDA granted accelerated approval of the drug for treating mantle cell lymphoma in patients who have received at least one prior therapy.¹⁹³ A second accelerated approval for treating CLL in patients who have received at least one prior therapy followed in February 2014.¹⁹⁴ In July 2014, FDA converted the accelerated approval of ibrutinib for treating relapsed/refractory CLL to a full approval, indicating that data from the phase III RESONATE trial "confirmed the drug's clinical benefit." Additionally, the FDA-approved indication for CLL was expanded to include a set of high-risk patients whose disease harbors a deletion on chromosome 17.¹⁹⁵ Lastly, in January 2015, FDA expanded ibrutinib's list of approved indications to include patients with Waldenström's macroglobulinemia.¹⁸⁶

Idelalisib was developed by Gilead Sciences, Inc. (Foster City, CA). In July 2014, FDA approved idelalisib for three types of recurrent/refractory NHL: CLL, small lymphocytic lymphoma, and follicular lymphoma.¹⁹⁶ Before these approvals, FDA had granted idelalisib breakthrough therapy status for treating patients with CLL.¹⁹⁷

Both ibrutinib and idelalisib are under study in a wide range of clinical trials that could lead to expansion of the range of NHLs and/or NHL treatment settings approved by FDA. In particular, use of these drugs could expand into earlier lines of treatment. For example, Abbvie recently reported that ibrutinib in combination with bendamustine and rituximab compared to bendamustine and rituximab alone improved progression-free survival, overall survival, and overall response rates in patients with previously untreated CLL; however, detailed results are not available.¹⁹⁸

Diffusion and cost: As of the second quarter of 2014 (about 4 months after approval for CLL and about 7 months after approval for mantle cell lymphoma), Pharmacyclics estimated that ibrutinib was being used by about 36% of patients undergoing treatment for recurrent/refractory CLL and by about 40% of patients undergoing treatment for recurrent/refractory mantle cell lymphoma.¹⁹⁹ Ibrutinib is taken on an ongoing basis until disease progression or unacceptable toxicity. According to GoodRx, the average retail price for 1 month of ibrutinib at the recommended dose for CLL (420 mg, once daily) is \$9,448, and for mantle cell lymphoma (560 mg, once daily) is \$12,772.^{200,201} Patients take the drug until disease progression or unacceptable toxicity. In clinical trials for treating CLL and mantle cell lymphoma, patients received ibrutinib treatment for a median of about 9 months;^{182,184} however, many patients were still taking ibrutinib at the cutoff for data analysis, and the real-world duration of treatment has not been established. In the phase II clinical trial in treating Waldenström's macroglobulinemia, patients received treatment for a median of about 19 months and 68% of patients were still receiving treatment at the time of the analysis.

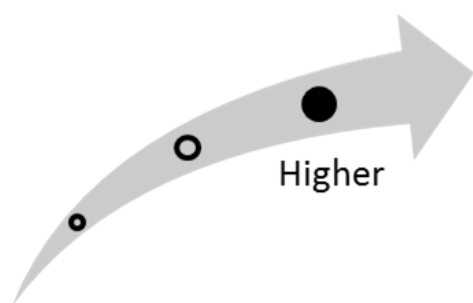
For the first quarter of 2015, Gilead reported \$26 million in worldwide idelalisib sales.²⁰² GoodRx listed an average retail price of \$3,773 for thirty 150-mg idelalisib tablets.²⁰³ At a recommended dosage of 150 mg twice daily, this represents a cost of approximately \$7,500 per month.¹⁹⁰ For treating patients with CLL, idelalisib is approved only as a combination therapy with the anti-CD20 monoclonal antibody rituximab. Combination therapy with idelalisib and rituximab could cost closer to \$12,000 per month with rituximab being administered during the first 5 months of treatment.^{190,204}

Our searches of 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found policies regarding ibrutinib and idelalisib that cover the drug according to labeled indications when certain conditions are met.²⁰⁵⁻²¹² These drugs are considered as specialty pharmaceuticals that require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

Treatment of B-cell NHLs is highly individualized, based on the subtype of NHL diagnosed in the patient, the patient's overall condition, and his or her response to any earlier lines of therapy. Treatments for CLL, indolent NHL, and mantle cell lymphoma include various combinations of cytotoxic agents, typically in combination with the monoclonal antibody rituximab. Other agents used in treating recurrent/refractory NHLs include alemtuzumab, lenalidomide, obinutuzumab, and ofatumumab for CLL; bortezomib and lenalidomide for mantle cell lymphoma; and alemtuzumab, bortezomib, everolimus, ofatumumab, and thalidomide for Waldenström's macroglobulinemia.^{213,214} Ibrutinib and idelalisib would represent additional treatment options for patients with recurrent B-cell NHL or certain patients with previously untreated NHL subtypes associated with poorer outcomes (e.g., patients with CLL harboring a chromosome 17 deletion).

Figure 7. Overall high-impact potential: ibrutinib (Imbruvica) and idelalisib (Zydelig) for treating non-Hodgkin's lymphomas



Overall, experts commenting on these interventions thought that a significant need exists for novel treatments of B-cell lymphomas and that the response rates observed in initial trials of ibrutinib and idelalisib indicated that the drugs have significant potential to improve patient outcomes. However, experts suggested that further study is needed to confirm this early promise, particularly studies comparing ibrutinib and idelalisib to alternative treatments. Experts thought that the relatively benign side-effect profile of these two drugs and their potential to be used for extended periods of time to treat several B-cell malignancies are significant. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Ibrutinib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of ibrutinib for treating CLL;²¹⁵⁻²²⁰ six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating mantle cell lymphoma;²²¹⁻²²⁶ and six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating Waldenström's macroglobulinemia.²²⁷⁻²³² One commenter offered perspectives on all three topics,^{215,231,233} and three commented on two topics;^{216,219,220,234-236} the rest commented on a single topic. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts commenting cited a moderate to high unmet need for new treatments for CLL, mantle cell lymphoma, and Waldenström's macroglobulinemia. However, several commenters noted that the relatively small number of patients affected by the diseases (particularly mantle cell lymphoma and Waldenström's macroglobulinemia) limits the magnitude of the unmet need. For CLL and mantle cell lymphoma, experts cited the propensity of these malignancies to recur and the lack of effective treatment options for patients with recurrent disease. In particular, one clinical expert noted the poor outcomes for patients with CLL whose disease harbors certain genetic mutations (i.e., 17p deletions).²¹⁵ One health systems expert who commented on ibrutinib's use in both CLL and mantle lymphoma and indicated use in the second-line setting limits ibrutinib's impact, and that studies demonstrating efficacy in the first-line setting could increase the magnitude of ibrutinib's impact.^{220,236} With regard to Waldenström's macroglobulinemia, experts noted the lack of FDA-approved treatment options for patients with the disease. Two experts with research and clinical perspectives who indicated the unmet need was only of minimal to moderate importance cited the fact that many off-label treatments are available.^{230,231} However, another clinical expert noted that despite the availability of these treatments, up to half of affected patients die of the disease.²³²

Ibrutinib's potential to improve health was also considered moderate to high by commenters, who noted the high response rates reported from phase II trials and the relatively tolerable adverse event profile of the treatment. Commenters who thought ibrutinib's potential to improve patient health was only moderate suggested that randomized controlled trials and longer-term outcomes would be needed to fully assess ibrutinib's effect on patient health. One clinical expert who thought ibrutinib's potential to improve patient health was high noted the significant unmet need presented by CLL harboring a chromosome 17 deletion (a subtype of CLL with poorer prognosis) and the preliminary evidence of ibrutinib's efficacy in this patient population.²¹⁵

Acceptance and adoption: Both clinicians and patients were seen by commenters as highly likely to adopt the use of ibrutinib. Factors encouraging adoption include the limited treatment options for patients with recurrent disease, ibrutinib's encouraging signs of efficacy and limited toxicity, and its ease of administration. However, several commenters suggested that the cost of ibrutinib might be unaffordable for some patients, and thus unadoptable.

Health system infrastructure and staffing: Ibrutinib is orally administered; therefore, most experts did not see its adoption as having a substantial impact on health care staffing or infrastructure. Some potential for change was envisioned if patients who might have received cytotoxic chemotherapy administered by infusion were instead treated with ibrutinib. Commenters noted that this would cause a shift in care setting and suggested that the mild side-effect profile observed thus far for ibrutinib could lessen the demand on health care providers to manage adverse events.

Health disparities: Commenters noted that disparities could be exacerbated for those unable to pay for the drug, because it is costly. One expert with a clinical perspective highlighted the issue of cost for patients with Waldenström's macroglobulinemia, citing the relatively long survival of this patient population and the potential that they could be taking a drug such as ibrutinib for an extended period.²³² Cost-driven increases in health disparities would be primarily an issue for the uninsured and those with high copayments, because third-party payers generally cover use of the drug for its FDA approved indications.

Idelalisib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of idelalisib for treating CLL,²³⁷⁻²⁴² and six experts, with similar backgrounds, offered perspectives on idelalisib for treating indolent NHL.²⁴³⁻²⁴⁸ Five experts commented on both topics;^{237,238,240-244,246-248} the rest commented on a single topic.

Unmet need and health outcomes: The majority of experts thought a moderate unmet need exists for better CLL and indolent NHL treatment; they cited the fact that treatments for these conditions are rarely curative and that options for patients with recurrent/refractory disease have limited efficacy. One clinical expert suggested that patients in whom intensive chemotherapy may be contraindicated (e.g., elderly patients, patients with coexisting conditions) have very limited treatment options.²³⁸

Idelalisib has moderate potential to improve health in patients with CLL or indolent NHL, according to the majority of experts commenting, who cited the promising data from initial trials and the mechanism of action. However, several commenters cited the preliminary nature of the data and that this left them unsure of the ultimate potential clinical benefit of the drug.^{241,242,248} One expert with a clinical perspective noted that adverse events (in particular colitis) could limit the duration of therapy. This commenter noted that this could complicate expansion of idelalisib use into the first-line setting.²³⁸

Acceptance and adoption: Both physicians and patients would likely adopt idelalisib, the experts thought, given limited treatment options, ease of oral administration, and preliminary promising data on efficacy. Experts who envisioned less widespread adoption again cited the preliminary nature of the data and suggested that some physicians and patients would want to await further data before opting for idelalisib. Additionally, experts envisioned that idelalisib's high cost could place a financial burden on patients and cause them to not use it or seek other options.

Health system infrastructure and staffing: As an orally administered drug, idelalisib is unlikely to change health care system infrastructure and staffing, according to the experts. A few suggested that displacing certain intravenously administered CLL and indolent NHL treatments by using idelalisib could shift patient care out of infusion centers; however, this was seen by most commenters as only a minor disruption to the health care system. Additionally, one clinical expert noted that introducing drugs such as idelalisib that are taken on an ongoing basis would cause a shift in patient management from episodic short-term therapy intended to induce temporary remissions to treatment of extended duration intended to manage the disease more like a chronic condition.²³⁸

Health disparities: Commenters noted that disparities could be exacerbated for those unable to pay for the drug, because it is likely to be costly and copayments may be high. In particular, multiple commenters noted that idelalisib could be taken on an ongoing basis by many patients, which could further increase costs relative to other CLL/indolent NHL treatments.

Ruxolitinib (Jakafi) for Treatment of Polycythemia Vera

Unmet need: Polycythemia vera is a rare myeloproliferative disorder that affects about 100,000 individuals in the United States.^{249,250} Patients with high-risk polycythemia vera are typically treated with a form of cytoreductive therapy that aims to prevent and manage thrombotic and bleeding complications, control symptoms, and minimize risk of progression to more aggressive diseases (e.g., post-polycythemia vera myelofibrosis, acute myeloid leukemia).²⁵¹ First-line treatment of high-risk polycythemia vera is typically hydroxyurea; however, for patients whose disease is not adequately controlled by hydroxyurea or patients cannot tolerate that treatment, a substantial unmet need exists for safe and effective therapies.²⁵²

Intervention: Ruxolitinib is an orally administered small-molecule inhibitor of two protein kinases (Janus kinase 1 and 2 [JAK1 and JAK2]) that play central roles in regulating myeloid lineages.²⁵³ Overactivation of Janus kinase pathway signaling has been linked to pathogenesis of polycythemia vera, and about 90% of polycythemia vera cases harbor an activating mutation in the gene encoding JAK2 (i.e., *JAK2V617F*).²⁵¹ JAK2 overactivity is also thought to play a key role in the pathophysiology of the related myeloproliferative neoplasm myelofibrosis, a condition in which ruxolitinib has demonstrated clinical utility.²⁵² On the basis of these observations, investigators have studied the potential use of ruxolitinib in treating patients who have polycythemia vera.

Clinical trials: Investigators studied ruxolitinib for treating patients with polycythemia vera in two phase III randomized control trials: RESPONSE and RELIEF.^{254,255} RESPONSE was an open-label trial in which patients (n=222) with polycythemia vera whose disease was resistant to hydroxyurea or who could not tolerate it were randomly assigned to receive ruxolitinib or best available therapy. Ruxolitinib was administered twice daily at a starting dose of 10 mg, which was titrated as needed (25 mg maximum). Best available therapy consisted of a physician's choice among hydroxyurea, pegylated interferon alfa, pipobroman, anagrelide, lenalidomide, pomalidomide, or phlebotomy. The trial's primary endpoint was the proportion of patients who achieved both hematocrit control without phlebotomy and a reduction in spleen volume of at least 35%. Investigators reported that the primary endpoint in the ruxolitinib and best available therapy arms was met in 21% and 1% of patients, respectively ($p<0.0001$).²⁵⁴

RELIEF was a double-blind trial in which patients (n=104) with polycythemia vera who were still reporting disease symptoms while on a stable hydroxyurea dose were randomly assigned to receive either ruxolitinib (dosed as in the RESPONSE trial above) or continued hydroxyurea. In each arm, patients also received a placebo matching the treatment in the alternate arm. The trial's primary endpoint was the percentage of patients at week 16 who achieved a 50% or greater reduction in the Myeloproliferative Neoplasm Symptom Assessment Form cytokine total symptom score (TSS-C), which measures patient-reported severity of symptoms (i.e., itching, tiredness, muscle ache, night sweats, and sweats while awake). Investigators reported that a "trend towards symptom improvement" was observed in patients assigned to ruxolitinib treatment, but it was not statistically significant; the percentage of patients achieving at least a 50% reduction in TSS-C from baseline to week 16 was 43.4% in the ruxolitinib arm and 29.6% in the hydroxyurea arm ($p=0.139$).²⁵⁵

Both hematologic and nonhematologic adverse events have been reported in patients taking ruxolitinib. The most common hematologic adverse events were thrombocytopenia and anemia. The most common nonhematologic adverse events were bruising, dizziness, and headache.²⁵⁶

Manufacturer and regulatory status: Ruxolitinib is being developed by Incyte Corp. (Wilmington, DE), in collaboration with Novartis International AG (Basel, Switzerland), which licensed the drug from Incyte for development and commercialization outside the United States.²⁵⁷

FDA approved ruxolitinib in 2012 for treating intermediate- or high-risk myelofibrosis, a myeloproliferative neoplasm related to polycythemia vera.²⁵⁶ In June 2014, Incyte submitted a supplemental new drug application (sNDA) to FDA, seeking a label expansion to include polycythemia vera in patients who have had an inadequate response to hydroxyurea or cannot tolerate it (the patient population enrolled in the RESPONSE trial).²⁵⁸ In December 2014, FDA approved ruxolitinib for treating “polycythemia vera patients who have an inadequate response to or cannot tolerate hydroxyurea.”²⁵⁹

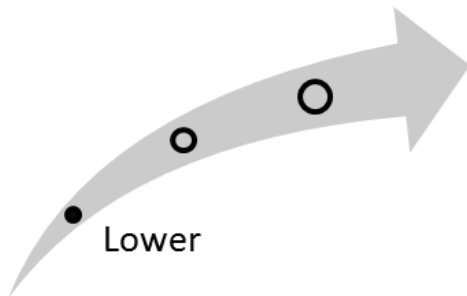
Diffusion and cost: GoodRx listed prices for ruxolitinib (sixty 10 mg tablets as a 1-month supply) as between \$9,707 and \$10,570 (average \$9,995).²⁶⁰ Higher- and lower-dose tablets (5–25 mg) were priced similarly. This represents a 1-month supply of the drug; therefore, 1 year of ruxolitinib treatment would cost about \$120,000.

A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified several payers that included ruxolitinib in their formularies.^{261–265} Plans typically classify ruxolitinib as a specialty pharmaceutical and require prior authorization for coverage.

Clinical Pathway at Point of This Intervention

Physicians manage symptoms of the disease by using phlebotomy to maintain a hematocrit level <45% and using aspirin to reduce risk of thrombosis. For patients with intermediate- to high-risk polycythemia vera, cytoreductive therapy may also be used. Patients may be designated as higher risk if they do not tolerate phlebotomy well, require frequent phlebotomies to maintain target hematocrit, have high platelet counts, or exhibit progressive leukocytosis. First-line cytoreductive therapies include hydroxyurea and interferon-alfa. For patients who are intolerant of or fail to respond to first-line therapy, alternatives include pipobroman and busulfan; however, these treatments are typically reserved for patients with shorter life expectancies because of their potential to lead to leukemia.^{251,252}

Figure 8. Overall high-impact potential: ruxolitinib (Jakafi) for treating polycythemia vera



Overall, experts commenting on this intervention believe that ruxolitinib has potential to meet a significant unmet need, given the significant morbidity that patients with polycythemia vera experience and the lack of approved treatments. In terms of improving health, a subset of commenters suggested ruxolitinib has substantial potential to improve treatments for patients with polycythemia vera, citing the efficacy demonstrated in the RESPONSE trial, the relatively benign safety profile, and the lack of existing safe and effective treatments. Conversely, other experts were more cautious about ruxolitinib’s potential, citing the lack of a statistically significant improvement in the RELIEF trial and the high cost of the drug as potential barriers to adoption. Based on these mixed perceptions on the part of experts commenting, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.²⁶⁶⁻²⁷⁰ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts commenting indicated that the need for novel treatments for polycythemia vera is moderately to very important, citing the significant morbidity experienced by patients with the disease and the previous lack of FDA-approved treatments. In particular, one clinical expert noted that hydroxyurea and other agents used off label in treating patients with polycythemia vera were mainly supportive (i.e., not disease-modifying) and did not prevent disease progression to more aggressive diseases such as myelofibrosis or leukemia.²⁶⁸

However, commenters were more varied in their opinions regarding ruxolitinib's potential to improve health outcomes in patients with polycythemia vera. Two experts suggested that ruxolitinib has moderate to large potential to improve patient health, citing the improved symptom control and reduction in need for phlebotomy observed in the phase III RESPONSE trial.^{268,269} Other commenters viewed the RESPONSE data less favorably, suggesting the data indicated limited efficacy,²⁶⁶ and several experts noted that ruxolitinib failed to reach statistical significance in a second phase III trial.

Acceptance and adoption: Moderate to wide adoption of ruxolitinib by clinicians and patients is likely, according to the majority of experts commenting. Factors promoting ruxolitinib adoption include convenience of oral administration, the lack of other polycythemia vera treatment options (particularly for patients who do not respond to existing treatments), and the manageable adverse-event profile.^{268,269} Factors that could limit ruxolitinib adoption include the high cost of the treatment and the unclear extent of ruxolitinib's benefit, given the preliminary nature of the data and the fact that only one of two phase III trials met its primary endpoint.^{266,270} Also, one clinical expert suggested that required twice-daily dosing could lead to adherence issues in some patients.²⁶⁸

Health care delivery infrastructure and patient management: Ruxolitinib would cause little to no change in health care facility staffing or infrastructure, according to experts commenting. They cited the oral medication's ease of administration, and one expert speaking from a clinical perspective suggested that the types of adverse events arising from ruxolitinib treatment could easily be managed in the outpatient setting.²⁶⁸

Health disparities: Ruxolitinib has no potential to improve health disparities, according to experts commenting. Several commenters suggested that its high cost could exacerbate existing health disparities based on socioeconomic status.

Siltuximab (Sylvant) for Treatment of Multicentric Castleman's Disease

Unmet need: Castleman's disease (also known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder that manifests as enlarged lymph nodes caused by accumulating nonclonal B cells.²⁷¹ Patients with multicentric Castleman's disease experience significant morbidity. Few treatment options are available, and disease recurrences are common.²⁷² Novel treatments are needed.

Intervention: Overproduction of the pleiotropic cytokine interleukin-6 (IL-6) has been implicated in the pathogenesis of Castleman's disease.²⁷² Evidence suggesting a role for IL-6 in Castleman's disease has come from multiple sources. Researchers have observed elevated levels of IL-6 in patients with the disease. Additionally, animal models in which IL-6 expression was experimentally elevated developed symptoms consistent with Castleman's disease. Lastly, a link between human herpes virus-8 (HHV-8) infection and Castleman's disease has been attributed to the production of a viral IL-6 ortholog, vIL-6 (an orthologous gene is one present in different species that evolved from a common ancestor).²⁷³ Basing their thinking on these observations, researchers have hypothesized that blocking the activity of IL-6 could ameliorate the symptoms of Castleman's disease.^{273,274}

Siltuximab is a chimeric monoclonal antibody for IL-6. Antibody binding to IL-6 may neutralize the cytokine, preventing it from exerting its pathogenic effects.²⁷⁴ In clinical trials for treating Castleman's disease, siltuximab is being administered in a 1-hour infusion at a dose of 11 mg/kg. Infusions are given once every 3 weeks, and the treatment may go on indefinitely, barring disease progression or unacceptable toxicity in the patient.^{275,276}

Clinical trials: Siltuximab was studied in a 79-patient, randomized, placebo-controlled, double-blind clinical trial in which patients were assigned in a 2:1 ratio to treatment with either siltuximab or placebo.²⁷⁷ Although Castleman's disease is frequently associated with HHV-8 infection in HIV-positive patients, HHV-8 and HIV-positive patients were excluded from the trial because siltuximab did not demonstrate binding to viral IL-6 in a preclinical trial.²⁷⁸ The primary endpoint of the trial was the number of patients who achieved a tumor response and a symptomatic response. In the trial, a higher percentage of patients in the siltuximab arm achieved a durable tumor and symptomatic response than did patients in the placebo arm (34% vs. 0%; $p=0.0012$). The rate of treatment-emergent adverse events was similar in the siltuximab and placebo group, despite patients receiving siltuximab for more than twice as long as patients receiving placebo (median 375 days vs. 152 days).²⁷⁷ Grade 3 or above adverse events were reported in 47% of patients receiving siltuximab versus 54% of patients receiving placebo, and severe adverse events were reported in 23% of patients receiving siltuximab versus 19% of patients.²⁷⁵ The most common adverse events that occurred at least 10% more often in patients receiving siltuximab than with placebo were hyperuricemia, increased weight, pruritus, rash, and upper respiratory tract infection.²⁷⁸

Manufacturer and regulatory status: Siltuximab was developed by the Janssen Biotech unit of Johnson & Johnson (New Brunswick, NJ). In April 2014, FDA approved siltuximab for treating patients "with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative."^{278,279} The siltuximab BLA was reviewed under FDA's priority review program.^{279,280}

Diffusion and cost: According to a May 2015 query of GoodRx, retail prices for 100 mg and 400 mg vials of siltuximab for infusion are about \$860 and \$3,600, respectively.^{281,282} A 70 kg (154 lb) adult at a dose of 11 mg/kg administered once every 3 weeks would require approximately two

400 mg vials per treatment, which would cost about \$7,000 per treatment. The drug is intended to be taken on an ongoing basis as long as the patient is benefitting from therapy.²⁷⁸

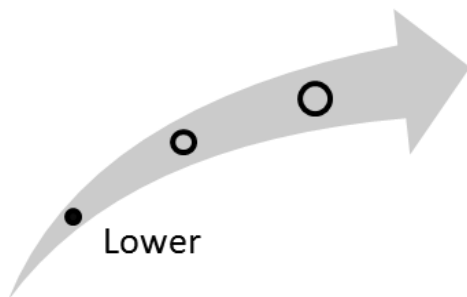
Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified 5 policies regarding siltuximab, which indicated that the drug is considered medically necessary and so covered for its FDA-approved indication.²⁸³⁻²⁸⁷ Two of these policies require prior authorization for coverage.^{284,285}

Clinical Pathway at Point of This Intervention

Before siltuximab was approved, no therapies had been FDA approved for treating multicentric Castleman's disease; however, many systemic therapies have been used off label. These have included traditional cytotoxic chemotherapy as well as more recent additions, such as the anti-CD20 monoclonal antibody rituximab and the immunomodulatory drug thalidomide.^{271,272}

Several antibodies targeting IL-6 signaling exist besides siltuximab. Although the majority of these compounds are investigational and, therefore, are not commercially available, one anti-IL-6-receptor antibody, tocilizumab, is FDA approved for another condition, rheumatoid arthritis. Preliminary studies of tocilizumab for treating Castleman's disease have been conducted, and the drug could be prescribed off label for this indication.²⁷³

Figure 9. Overall high-impact potential: siltuximab (Sylvant) for treatment of multicentric Castleman's disease



Overall, experts commenting on this intervention concurred that siltuximab has potential to fill a significant unmet need of patients with multicentric Castleman's disease, given results from a clinical trial and the fact that FDA has approved no other therapies for this indication. However, siltuximab's overall impact is limited by the small size of the affected patient population, the lack of any substantial changes to patient management and health care facility infrastructure, and the preliminary nature of the data on a therapy that could potentially be taken for extended periods. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this topic.²⁸⁸⁻²⁹³ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for novel therapies to treat Castleman's disease is moderately to very important according to experts commenting, who cited the lack of FDA-approved therapies for the condition and its significant morbidity. Although one health systems commenter suggested that the availability several off-label treatments for treating patients

with multicentric Castleman's disease limits the magnitude of the unmet need,²⁸⁸ other commenters with clinical perspectives noted that no reliable treatment exists for this patient population and that available treatments are often associated with substantial toxicity, which limits their long-term use for an individual.^{291,292} Although most commenters noted the lack of effective therapies, the majority also noted that the small number of patients affected by this condition limits the magnitude of unmet medical need overall.

Siltuximab has minimal to moderate potential to improve patient health, according to experts' comments. Although commenters suggested that the phase II trial results that led to FDA approval were promising in terms of response rate, several commenters noted that this came at the expense of prolonged and sometimes severe adverse events. Experts were divided in their opinions regarding the risk-benefit profile of the treatment, with two suggesting the drug has only minimal potential to improve patient health^{288,292} and two suggesting that its potential was moderate.^{289,291} One expert with a research perspective noted that treatment may involve long-term therapy and, therefore, longer-term studies of the treatment's impact on patient outcomes and quality of life are needed.²⁹³

Acceptance and adoption: Siltuximab is likely to be adopted by clinicians and patients, thought the majority of experts. These experts noted that the lack of viable alternatives (in particular FDA-approved alternatives) and siltuximab's familiar mode of IV infusion as factors promoting clinician adoption. Additionally, one clinical expert noted that patients would be attracted to a treatment that has the potential for durable symptom control.²⁹¹ However, a second clinical expert suggested that some patients could be dissuaded from the treatment because it requires ongoing infusions administered once every 3 weeks.²⁹² One commenter with a health systems perspective suggested that siltuximab adoption would be minimal because of the potential for adverse events and the availability of off-label alternatives.²⁸⁸

Health care delivery infrastructure and patient management: Siltuximab use would cause little to no change in health care facility staffing or infrastructure, the experts thought. They cited the familiar mode of IV infusion and fact that patients with the disease are likely to have already received off-label IV treatments for the disease. Furthermore, experts thought that the small number of patients with multicentric Castleman's disease would limit any potential impacts in health care delivery and infrastructure.

Health disparities: The relatively high cost of siltuximab, combined with the need to receive infusions for an extended period of time, led commenters to conclude that adopting siltuximab would increase the cost of care for this patient population. This new therapy may exacerbate health disparities between the uninsured or underinsured because it may be unaffordable to patients with limited economic means.

Lung Cancer Intervention

Nivolumab (Opdivo) for Treatment of Nonsmall Cell Lung Cancer

Unmet need: Despite recent advances in targeted therapeutic agents that can be used in combination with platinum-based chemotherapy, prognosis and outcomes in patients with lung cancer are poor, and lung cancer remains the leading cause of cancer-related deaths in the world.²⁹⁴ In the United States, patients who have advanced nonsmall cell lung cancer (NSCLC) have a 5-year survival rate of 2% to 13%. Clearly, novel approaches are needed.²⁹⁵

Researchers have observed the potential of the immune system to be a tool to treat cancer.²⁹⁶⁻²⁹⁸ One approach under study is the inhibition of so-called immune checkpoints, which purportedly suppress anticancer immune responses. Nivolumab (Opdivo®) is a monoclonal antibody that targets the programmed death-1 (PD-1) receptor, a component of one such immune checkpoint pathway. Several clinical trials are testing nivolumab as monotherapy or in combination with chemotherapy for treating NSCLC.²⁹⁹⁻³⁰²

Intervention: Researchers have identified several strategies cancer cells have developed to avoid detection and destruction by the body's immune system.^{303,304} One such immune-tolerance mechanism involves tumor cells overexpressing ligands that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers reportedly can reduce the body's anti-cancer immune response.³⁰⁴

One of these checkpoint pathways is PD-1, a cell receptor expressed by many immune-system cells, including high expression on activated T cells, which has a central role in T-cell downregulation.³⁰⁴ Research has demonstrated that in many cases, the ligand for PD-1 (PD-L1) is highly expressed by the tumor microenvironment. Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response.³⁰⁵ Disrupting the immune tolerance—inducing signaling between tumor-expressed PD-L1 and immune cell—expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” placed on the immune response through the PD-1 signaling pathway.³⁰⁴

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1. Preclinical studies performed in cancer animal models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response.^{306,307} Nivolumab binding to PD-1 purportedly prevents the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.^{299-302,306,308,309}

Nivolumab is administered by IV infusion. In phase I clinical trials, researchers tested escalating doses of nivolumab by using concentrations ranging from 0.3 to 10 mg/kg.^{306,310} In ongoing phase III trials, patients with NSCLC are treated with 3 mg/kg of nivolumab administered once every 2 weeks.^{300,301}

Clinical trials: The CheckMate trial program is testing nivolumab in the second-line setting for treating advanced/metastatic squamous NSCLC (CheckMate 017 and 153) or nonsquamous NSCLC (CheckMate 057) in patients whose disease has failed to respond to systemic platinum-based doublet chemotherapy. Nivolumab is also being studied as first-line treatment for therapy-naïve patients with advanced/metastatic NSCLC who are positive for PD-L1 expression (CheckMate 026).

The phase III CheckMate 017 and CheckMate 057 trials are randomized, open-label trials of 272 patients with squamous NSCLC and 574 patients with nonsquamous NSCLC, respectively. Patients received intravenously administered nivolumab (3 mg/kg, once every 2 weeks) or

intravenously administered docetaxel (75 mg/m², once every 3 weeks), and results from both trials were presented at the 2015 ASCO annual meeting.^{311,312} In the CheckMate 017 trial, a superior overall survival was observed in patients receiving nivolumab compared with those receiving docetaxel (9.2 months with nivolumab vs. 6.0 months with docetaxel; HR, 0.59; p=0.00025). Similarly, nivolumab also improved progression-free survival (3.5 months with nivolumab vs. 2.8 months with docetaxel; HR, 0.62; p=0.0004) and response rate (20% with nivolumab vs. 9% with docetaxel; p=0.0083).³¹³ In January 2015, an independent data monitoring committee concluded that the CheckMate 017 trial had met its endpoint and recommended treating all patients in both groups with nivolumab.^{314,315}

Data from the CheckMate 057 trial also demonstrated a significant improvement in overall survival and response rate compared with docetaxel (overall survival, 12.2 months with nivolumab vs. 9.4 months with docetaxel; HR, 0.73; p=0.00155; response rate, 19.2% with nivolumab vs. 12.4% with docetaxel; p=0.0235). In contrast, nivolumab did not demonstrate clinical benefit in progression-free survival (2.3 months with nivolumab vs. 4.2 months with docetaxel; HR, 0.92; p=0.393), which may be associated with PD-L1 expression.³¹⁶

Potential safety concerns for patients may include the following drug-related toxicities reported in the phase I MDX-1106-03 trial, in which patients were treated with 1, 3, or 10 mg/kg of nivolumab:³⁰⁶

- Infusion-related reaction (10%)
- Diarrhea (9%)
- Pruritus (6%)
- Hypothyroidism (3%)
- Pruritic rash (2%)
- Vitiligo (2%)
- Adrenal insufficiency (1%)
- Erythema (1%)
- Erythematous rash (1%)
- Macular rash (1%)

Similar to other immunotherapies, nivolumab has the potential to lead to autoimmune or other immune-system disorders, which were observed in 81 of 207 patients (39%) and included rash, autoimmune thyroiditis, hepatitis, and one case each of sarcoidosis, endophthalmitis, diabetes mellitus, and myasthenia gravis.³⁰⁶ When nivolumab was administered at a single dose of 3 mg/kg once every 2 weeks, a decrease in the incidence of serious drug-related adverse events was observed, as compared with patients in the phase I MDX-1106-03 trial. The most common nivolumab-related toxicities reported in the phase II CheckMate 063 trial included fatigue (4%), diarrhea (3%), pneumonitis (3%), anemia (1%), myalgia (1%), pruritus (1%), and rash (1%).³¹⁷

Manufacturer and regulatory status: Nivolumab is being developed by Bristol-Myers Squibb (New York, NY) for treating various types of cancer. After granting priority review in February 2015, FDA approved nivolumab in March 2015 under its accelerated approval program for treating patients with metastatic NSCLC that has progressed after treatment with platinum-based chemotherapy.^{315,318} FDA approval was based on overall survival benefit observed in the phase III CheckMate 017 trial and the safety profile observed in the phase II CheckMate 063 trial.³¹⁵

Nivolumab was FDA-approved in December 2014 for treating advanced melanoma not responsive to ipilimumab or a *BRAF* inhibitor if the disease has the *BRAF*^{V600} mutation.^{319,320} In 2013, FDA had granted the drug fast-track status for treating NSCLC, melanoma, and renal cell carcinoma.³²¹

Diffusion and cost: A May 2015 query of GoodRx listed costs of about \$2,500 for a 100 mg vial of nivolumab.³²² The prescription information states nivolumab is administered at a dose of 3 mg/kg every 2 weeks.³²³ Therefore, a patient weighing an average of 70 kg would require 210 mg (about 2 vials) costing \$5,250 per infusion, which would total approximately \$136,500 per year.

The U.S. Centers for Medicare & Medicaid Services has not issued a national coverage determination for nivolumab. Thus, coverage decisions are left to the discretion of local Medicare carriers. Our searches of 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches identified four policies that cover nivolumab for treating NSCLC that has progressed after platinum-based doublet chemotherapy; other policies probably had not been updated for the recent NSCLC indication.³²⁴⁻³²⁷ Drugs intended to treat cancer are typically covered for their FDA-approved indications. Therefore, use of nivolumab in treating metastatic NSCLC will likely be covered by many third-party payers.

Clinical Pathway at Point of This Intervention

Treatment for NSCLC depends on the patient's condition, the cancer stage, tumor histology, and whether genetic alterations that may have triggered the oncogenic process have been identified in the patient's cancer. For advanced/metastatic NSCLC, various systemic treatments are used.

The most common first-line chemotherapy is platinum-doublet therapy, in which carboplatin or cisplatin is combined with paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, or pemetrexed.³²⁸

Combining platinum-based chemotherapy with targeted interventions is also an effective approach for treating NSCLC. In NSCLC, blood vessel formation (angiogenesis) and EGFR signaling are highly upregulated, and drugs that target these pathways have been developed.^{294,329} One of these drugs, bevacizumab, is a monoclonal antibody that inhibits angiogenesis by binding and blocking the activity of VEGF.³²⁸ Recent clinical data have also shown that combining platinum-based chemotherapy with ramucirumab, another angiogenesis-blocking antibody, can improve overall survival and progression-free survival in patients with NSCLC.³³⁰ The EGFR inhibitor cetuximab can also be used as an adjunct to platinum-based therapy.

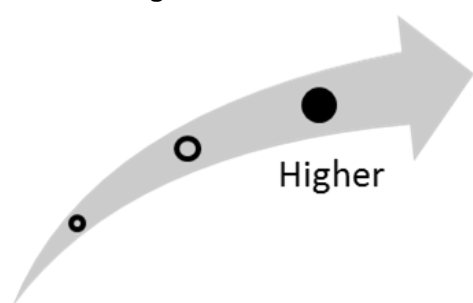
In the case of cancers bearing an activating mutation in the *EGFR* or the *ALK* gene, EGFR inhibitors (e.g., erlotinib, afatinib, gefitinib) or ALK inhibitors (e.g., crizotinib, ceritinib) may be considered as a monotherapy.^{328,331,332} These genetic drivers occur more frequently in nonsquamous cancers; therefore, cancers with squamous histology may not routinely undergo genetic analysis. In the event that NSCLC continues to grow or spread after these first-line treatments, patients may be switched to a different cytotoxic chemotherapy (e.g., docetaxel, gemcitabine, erlotinib, pemetrexed).³²⁸

Nivolumab is under study in the three following treatment settings:

- First-line treatment of advanced/metastatic NSCLC that is positive for PD-L1 expression (CheckMate 026 trial)
- Second-line treatment of advanced/metastatic squamous NSCLC (CheckMate 017 and CheckMate 153 trials)
- Second-line treatment of advanced/metastatic nonsquamous NSCLC (CheckMate 057 trial)

Although nivolumab has been approved by FDA for treating melanoma and NSCLC, several companies are developing and testing PD-1/PD-L1-specific monoclonal antibodies (e.g., pembrolizumab, MEDI4736, MPDL3280A) for treating NSCLC as well as other cancer types, including melanoma, head and neck cancers, and renal cell carcinoma.^{319,320,333-335}

Figure 10. Overall high-impact potential: nivolumab (Opdivo) for treatment of nonsmall cell lung cancer



Overall, most experts commenting on this intervention think nivolumab has significant potential to improve outcomes in patients with NSCLC, who currently have limited treatment options. Further, if results from additional studies continue to be favorable and the role of PD-L1 in cancer is better understood, nivolumab has the potential to offer more benefit than standard treatments. If the available clinical data suggest it can be a novel option for treatment-resistant NSCLC, experts anticipate, nivolumab will be widely adopted by physicians and patients. Because it is administered intravenously, nivolumab will affect neither health care infrastructure nor patient management. In a contrasting opinion, some experts thought that the onset of serious adverse events caused by immunotherapy could be a hurdle for adoption. Experts also agree nivolumab is very expensive and has a high potential to affect health care costs; whether costs will be absorbed mostly by third-party payers or patients remains to be determined because it will depend on coverage and any discounts negotiated by payers with the company. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.³³⁶⁻³⁴¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Patients with NSCLC have a 5-year survival rate ranging between 2% and 13% and most die within the first year of diagnosis, so all experts agreed a great need exists for targeted options that improve survival over systemic therapies. One expert thought nivolumab would be favorable in tumors overexpressing PD-L1, in particular because some evidence shows nivolumab improves survival in patients with other types of cancer.³³⁶ Even though one expert did not think nivolumab had a strong potential to improve outcomes based on the available data, others thought the results from a study that was stopped early due to a survival advantage would demonstrate the potential of nivolumab to address an unmet need.³³⁷⁻³⁴⁰ Despite promising overall survival rates, a health systems expert was concerned about comorbidities nivolumab may cause.³⁴¹

Acceptance and adoption: Most experts concurred that physicians and patients would readily adopt nivolumab for treating NSCLC because of its potential to extend survival and routine administration route. Severe adverse events could be a barrier for acceptance, opined an expert,³³⁶ although another expert argued the survival benefits could outweigh adverse events and complications.³⁴¹

Health care delivery infrastructure and patient management: Experts agreed that nivolumab would not disrupt treatment delivery or patient management. But if nivolumab showed a significant benefit, infrastructure would have to expand to accommodate more patients, an expert thought.³³⁸ It is given as an IV infusion, and experts concurred that health centers offering IV treatments would

already have the infrastructure to provide Nivolumab and that patient management would remain the same because NSCLC patients already receive IV treatments, and nivolumab would simply be another offering.³³⁹ Because of improved patient survival, however, oncologists would need to monitor patients longer term for serious adverse events, an expert suggested.³⁴¹

Health disparities: Because NSCLC affects various patient populations, a clinician did not anticipate nivolumab would affect health disparities.³⁴⁰ In contrast, three experts thought the very high price of nivolumab could increase disparities in patients with low socioeconomic status.^{337,339,341} Additionally, people living in poverty have a higher exposure to smoking, asbestos, and air pollution, another expert pointed out.³³⁸ Even if nivolumab is covered by insurance, its high price of about \$136,500 per year will significantly increase health care costs and co-pays would be high. Three experts emphasized the fact that NSCLC is the second most common cancer, which would increase the cost burden to third-party payers and patients in the form of higher copayments and deductibles.³³⁹⁻³⁴¹

Skin Cancer Interventions

Nivolumab (Opdivo) and Pembrolizumab (Keytruda) for Treatment of Advanced Melanoma

Unmet need: Despite recent advances in treatment options for melanoma, many patients in whom advanced melanoma has been diagnosed have a poor prognosis, and new treatments are needed. Recent phase III clinical trials with the anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) monoclonal antibody, ipilimumab (Yervoy®), demonstrated the potential of immune system checkpoint inhibitors to produce durable responses in patients with advanced melanoma by activating the body’s immune system.^{297,298} However, only a minority of patients experience such a response, and new approaches to stimulate immune responses to melanoma are highly sought. One approach targets the PD-1 receptor, a second immune checkpoint pathway that purportedly suppresses the anti-melanoma immune response. Several molecules targeting PD-1 or PD-1 ligands are under study in clinical trials for treating melanoma, including the PD-1–specific monoclonal antibodies nivolumab (Opdivo®) and pembrolizumab (Keytruda®).^{304,342,343}

Intervention: Evading destruction by the body’s immune system is a hallmark of cancer, and researchers have identified several mechanisms by which cancers induce immune tolerance.^{303,304} One such mechanism is the cooption by tumors of endogenous mechanisms that limit T-cell responses. These so-called immune checkpoints are thought to have evolved to prevent runaway immune responses; however, by aberrantly activating these immune checkpoints, cancers purportedly can reduce the body’s anticancer immune response.³⁰⁴

PD-1 is a central player in one of these checkpoints.³⁰⁴ PD-1 is expressed by many cells of the immune system, including high expression levels on activated T cells. Research has demonstrated that in many cases, the tumor microenvironment expresses a ligand for PD-1 (PD-L1). Binding of PD-L1 to PD-1 is thought to induce T-cell anergy (diminished response to persistent antigen exposure), limiting tumor rejection by tumor-specific T cells in the effector phase of the immune response.³⁰⁵ Disrupting the immune tolerance–inducing signaling between tumor-expressed PD-L1 and immune cell–expressed PD-1 is a therapeutic target that could potentially induce an immune response to the cancer by “releasing a brake” placed on the immune response through the PD-1 signaling pathway.³⁰⁴

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1.³⁰⁷ Similarly, pembrolizumab is a humanized monoclonal antibody in which the Fc region has been modified to reduce the induction of antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, which have the potential to deplete immune cells expressing PD-1.³⁴³ Preclinical studies performed in animal cancer models have shown that antibody-mediated inhibition of the PD-1/PD-L1 pathway increases T-cell antitumor response.³⁰⁶ Nivolumab and pembrolizumab binding to PD-1 purportedly prevent the interaction between PD-1 and its ligands, preventing activation of the immune checkpoint and leading to an increase in anticancer immune response.³⁰⁶

Nivolumab and pembrolizumab are administered by IV infusion. In phase I trials, researchers tested escalating doses of nivolumab for various cancers, infusing doses ranging from 0.3 to 10 mg/kg.^{306,310} In ongoing phase III trials, patients with melanoma are given 3 mg/kg of nivolumab once every 2 weeks.³⁴⁴⁻³⁴⁷ Pembrolizumab, which FDA recently approved, has prescribing information recommending 2 mg/kg once every 3 weeks, and treatment may continue for up to 2 years.^{348,349}

Clinical trials: Nivolumab and pembrolizumab are being tested primarily as immunotherapy for advanced melanoma and NSCLC.^{299-302,308,309,345-348,350} Investigators have also initiated clinical trials of nivolumab and pembrolizumab for treating triple-negative breast cancer, head and neck cancer, urothelial tract cancer, gastric cancer, and blood cancers.^{306,310,351,352}

In September 2014, results from the phase III CheckMate-037 trial were presented at the European Society of Medical Oncology Annual Meeting. In this study, patients with metastatic melanoma whose disease had progressed after ipilimumab treatment were given nivolumab (n=120) or investigator's choice of chemotherapy (n=47). The objective response rate was compared between groups. An independent review committee reported that patients who were treated with 3 mg/kg nivolumab had a significantly higher objective response rate (32%; 95% CI, 24% to 41%) than patients who received chemotherapy (11%; 95% CI, 3.5% to 23%). Conversely, grade 3–4 adverse events were less frequent after treatment with nivolumab (9%) than after chemotherapy (31%).³⁵³

The nivolumab's efficacy in untreated patients with unresectable advanced melanoma bearing the wild-type *BRAF* gene was evaluated in the phase III CheckMate-066 trial. Authors published results (n= 418) in January 2015 reporting that after 1 year of treatment with nivolumab, overall survival and progression-free survival improved significantly compared to patients treated with dacarbazine. Overall survival in the nivolumab group was 73% (95% CI, 65% to 79%) and in the dacarbazine group, it was 42% (95% CI, 33% to 51%). The median progression-free survival in the nivolumab group was 5.1 months versus 2.2 months in the dacarbazine group (HR, 0.43; 95% CI, 0.34 to 0.56; p<0.001). Grade 3–4 adverse events occurred in 11.7% of patients treated with nivolumab and 17.6% of patients treated with dacarbazine. The most common nivolumab-related adverse events were fatigue, pruritus, and nausea.³⁵⁴ In June 2014, the manufacturer announced that the CheckMate 066 trial would be stopped and unblinded ahead of schedule because of a significant benefit observed in patients treated with nivolumab compared with dacarbazine. Patients receiving the latter treatment were offered nivolumab in an open-label extension of the study.³⁵⁵

Results were reported in May 2015 from CheckMate 067, a phase III randomized, double-blind, controlled trial assessing the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in treatment-naïve patients with unresectable advanced melanoma. Nivolumab plus ipilimumab showed a superior clinical benefit over nivolumab or ipilimumab monotherapy. The median progression-free survival was 11.5 months in the nivolumab plus ipilimumab group (HR, 0.42; 99.5% CI, 0.31 to 0.57; p<0.001) and 6.9 months in the nivolumab group (HR, 0.57; 99.5% CI, 0.43 to 0.76; p<0.001), compared to 2.9 months in the ipilimumab group. However, a higher rate of grade 3 and 4 treatment-related adverse events were observed in patients who received nivolumab plus ipilimumab (55%) than in those treated with nivolumab (16%) or ipilimumab (27%) alone.³⁵⁶

Results from KEYNOTE-001 were published in July 2013. Investigators in this phase I, open-label trial of 135 patients with advanced melanoma reported that a regimen of 10 mg/kg pembrolizumab administered every 2 weeks had the highest response rate (52%; 95% CI, 38% to 66%) relative to other dosages. No significant difference was observed in the response rate between patients who had previously received ipilimumab (38%; 95% CI, 23% to 55%) and those who had not (39%; 95% CI, 26% to 49%). The most common pembrolizumab-related adverse events included fatigue, rash, pruritus, and diarrhea; side effects were reported in 79% of patients. Of the total number experiencing side effects, 13% of patients experienced grade 3 or 4 adverse events.³⁵⁷

In April 2015, results from the phase III KEYNOTE-006 trial were published. In this open-label study, 834 patients with advanced melanoma were randomly assigned to one of three groups, 1:1:1, to receive IV pembrolizumab (10 mg/kg) every 2 weeks or every 3 weeks until disease progression, or 4 doses of IV ipilimumab (3 mg/kg) every 3 weeks. At 6 months, the progression-free survival rates after treatment with pembrolizumab were 47.3% for every 2 weeks and 46.4% for every 3 weeks, as compared with 26.5% for ipilimumab (HR, 0.58; 95% CI, 0.46 to 0.72 for 2 weeks of treatment and HR, 0.58; 95% CI, 0.47 to 0.72 for 3 weeks of treatment). Similarly, after 1 year, patients treated with pembrolizumab had a higher survival rate than patients treated with ipilimumab, which were 74.1% for 2 weeks (HR, 0.63; 95% CI, 0.47 to 0.83; p<0.0005) and 68.4%

for 3 weeks (HR, 0.69; 95% CI, 0.52 to 0.90; $p < 0.0036$) when compared with 58.2% for ipilimumab. Patients who received ipilimumab experienced a higher rate of grade 3–5 treatment-related adverse events (19.9%) than patients receiving either pembrolizumab regimen (every 2 weeks, 13.3%; every 3 weeks, 10.1%).³⁵⁸ In March 2015, the manufacturer announced the phase III KEYNOTE-006 trial had met its coprimary endpoints of progression-free survival and overall survival. Additionally, the trial was stopped early after an independent data monitoring committee confirmed that pembrolizumab improved on overall survival and progression-free survival, as compared with ipilimumab.³⁵⁹

Manufacturer and regulatory status: Nivolumab is being developed by Bristol-Myers Squibb (New York, NY). After granting priority review under the Prescription Drug User Fee Act in September 2014, FDA approved nivolumab under its accelerated approval program in December 2014 for treating patients with advanced melanoma after treatment with ipilimumab or a BRAF inhibitor if patients bear the *BRAF*^{V600} mutation.^{319,320} Additionally in April 2015, FDA accepted a supplemental new drug application for nivolumab in the first-line setting for treating advanced melanoma.³⁶⁰ Nivolumab was also granted fast-track designation by FDA in 2013 for treating melanoma, NSCLC, and renal cell carcinoma and in March 2015 was approved for treating recurrent NSCLC.^{318,321}

Pembrolizumab is being developed by Merck & Co., Inc. (Whitehouse Station, NJ). In September 2014, FDA approved pembrolizumab for treating unresectable or metastatic melanoma in patients whose disease has progressed after treatment with ipilimumab or, if melanoma was *BRAF*^{V600} mutation–positive, a BRAF inhibitor.³⁶¹ Pembrolizumab was approved on the basis of tumor response rate and durability of response; therefore, the approved indication is contingent upon clinical studies demonstrating improved survival and disease-related symptoms.^{361,362} FDA had earlier granted pembrolizumab breakthrough therapy status for treating advanced melanoma.³⁶³

Diffusion and cost: Upon approval of nivolumab in Japan, Ono Pharmaceutical Co. (Osaka, Japan), the company with distribution rights in Japan, Korea, and Taiwan, released an estimated cost of \$1,459 for a 20 mg vial of nivolumab.^{364,365} In the United States, however, based on a query of GoodRx in May 2015, the cost of nivolumab is about \$2,500 for a 100 mg vial. Therefore, a single infusion for a 70 kg patient at the typical dose of 3 mg/kg would cost about \$5,250, adding up to \$136,500 per year.³²²

A query of GoodRx found costs of pembrolizumab as of May 2015 of about \$6,600 for 3 vials of 50 mg, which at a dose of 2 mg/kg every 3 weeks is roughly the amount (about 150 mg) a patient would use for a single treatment cycle.³⁶⁶ Thus, if a patient continued on treatment for a full year, the cost would be about \$112,200 (17 cycles at \$6,600 per cycle).

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark). Our searches found six third-party payers with policies that consider nivolumab and pembrolizumab to be medically necessary for treating melanoma and will offer coverage if specific criteria are met.^{324-327,367-373} Like other IV cancer drugs, PD-1 inhibitors are considered specialty medications that are not self-administered and will require preauthorization for coverage. Pembrolizumab is available through a manufacturer-sponsored expanded-access program to select patients who do not have health insurance, who have health plans that do not cover pembrolizumab, or who have coverage but cannot afford copayments.³⁷⁴

Clinical Pathway at Point of This Intervention

To systematically treat advanced melanoma, clinicians weigh the three following options: immunotherapy, targeted therapy for melanoma that harbors specific genetic changes, and cytotoxic chemotherapy. According to National Comprehensive Cancer Network guidelines for treating melanoma, preferred systemic treatment options include the following:³⁷⁵

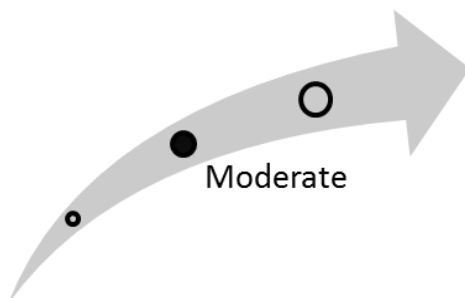
- BRAF inhibitor (i.e., dabrafenib or vemurafenib) for patients with BRAF mutation–positive melanoma
- Dabrafenib plus the MEK inhibitor trametinib for patients with BRAF mutation–positive melanoma
- High-dose interleukin-2
- Ipilimumab

PD-1 checkpoint inhibitors have the potential to compete with existing treatments for advanced melanoma. In clinical trials, nivolumab and pembrolizumab have been and are being tested head-to-head with ipilimumab in first- or second-line treatment of patients with advanced melanoma and head-to-head with cytotoxic chemotherapy in patients with advanced melanoma previously treated with ipilimumab. Nivolumab is also being tested as immunotherapy given before or after treatment with the BRAF inhibitor dabrafenib plus trametinib in patients with BRAF mutation–positive melanoma.^{304,344-347,376} Additionally, other companies are developing and testing PD-L1–specific monoclonal antibodies (e.g., MEDI4736, MPDL3280A) for treating melanoma as well as other cancer types, including NSCLC, head and neck cancers, and renal cell carcinoma, which could also compete with nivolumab and pembrolizumab if the drugs in this class are approved.^{334,335}

Antibodies specific against PD-1 might also be used as part of combination therapy. For example, recently reported results from a small trial of the combination of ipilimumab and nivolumab demonstrated substantial activity in advanced melanoma.³⁴² Additionally, Merck recently announced plans for trials of pembrolizumab in combination with various agents not yet approved by FDA, including the viral immunotherapy talimogene laherparepvec.³⁷⁷

An additional technology that may be used in concert with anti-PD1 antibodies is a genomic test that could identify levels of PD-L1 expression by tumors. The mechanism of action of PD-1 antibodies suggests that they may be more efficacious in patients whose tumors express high levels of PD-L1.³⁰⁴ However, ongoing trials of pembrolizumab and nivolumab in melanoma are not selecting patients on the basis of this marker.

Figure 11. Overall high-impact potential: nivolumab (Opdivo) and pembrolizumab (Keytruda) for treatment of advanced melanoma



Nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma treatment, some experts thought, attributing their assessment to scarce safety and efficacy data and a similar mechanism of action to that of approved and other soon-to-be-approved melanoma therapies. However, other experts regarded nivolumab and pembrolizumab as having high-impact potential to fulfill the unmet need because it can be used as second-line treatment in patients with very poor

prognoses whose disease has relapsed after treatment with ipilimumab or BRAF inhibitors. Because of the lack of options for this patient population, PD-1 inhibitors are expected to be adopted by both clinicians and patients, thought the experts, who also did not anticipate the drugs would have significant impacts on infrastructure, patient management, or health disparities. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on nivolumab for treating advanced melanoma,³⁷⁸⁻³⁸³ and six experts, with similar backgrounds, offered perspectives on pembrolizumab for treating advanced melanoma.³⁸⁴⁻³⁸⁹ Of these, one commented on both nivolumab and pembrolizumab.^{388,390} We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists for new treatments for patients with advanced melanoma, the experts agreed. Despite some experts stating that preliminary data are not sufficient to determine whether these drugs will effectively address this need, most agreed that more targeted therapies, such as PD-1 inhibitors, are needed to close the gap for patients whose melanoma does not respond to other therapies. This same group of experts also believes that efficacy data on nivolumab and pembrolizumab show potential to improve response rates and extend survival.^{382,383,389} PD-1 antibodies could improve patient health and decrease the cost of standard therapies, was the opinion of an expert with research experience. However, an expert also argued the development of antibodies against PD-L1 could increase the number of drugs in the field and decrease the importance of pembrolizumab for treating melanoma.³⁸⁷

Acceptance and adoption: Although a couple of experts were concerned that pembrolizumab would be adopted only when clinical data prove it to be better than similar treatments, most experts agreed that PD-1 inhibitors would be readily and easily adopted by both physicians and patients on the basis of available data, its routine administration route (IV), and a safety profile suggesting its adverse events are no worse than similar anticancer agents.^{386,387} Advanced melanoma progresses rapidly; thus, any drug capable of slowing progression of refractory disease will be welcomed for treating melanoma, two clinical experts noted.^{382,384}

Health care delivery infrastructure and patient management: As intravenously administered agents, nivolumab and pembrolizumab are not expected to affect health care delivery or infrastructure, noted the experts. They do not anticipate much impact on patient management other than the fact that patients now have an option when ipilimumab stops working.³⁸² A research expert thought that in contrast to the oral medication vemurafenib (Zelboraf®), pembrolizumab use will shift more patients to infusion clinics for treatment.³⁸⁸

Health disparities: Overall, PD-1 inhibitors are not expected to affect health disparities, although experts are concerned about the high cost of these drugs and thought they could increase health disparities because of high co-pays. On the other hand, experts also pointed out that current melanoma treatments are also very costly and speculated that as a cancer treatment, the two drugs will probably will be covered by insurance. Additionally, the incidence of melanoma is greater in fair-skinned individuals, so usage would likely be higher in this group than in other groups that have a lower incidence of melanoma, opined a clinician.³⁸²

Talimogene Laherparepvec (T-VEC) for Treatment of Advanced Melanoma

Unmet need: Patients with unresectable, advanced or metastatic melanoma have an extremely poor prognosis. Although recently approved treatments have provided much-needed options for patients with advanced disease, available treatments have limited response rates and/or short response duration because patients acquire drug resistance.³⁹¹ Additionally, many existing therapies are associated with considerable toxicity. Novel approaches for treating advanced melanoma are greatly needed.

Several novel oncolytic therapies have recently reached late-stage development. If approved, one of these—talimogene laherparepvec (T-VEC)—would be a first-in-class oncolytic viral therapy for melanoma that would provide a new option for patients who may have exhausted existing options. Because T-VEC exerts its effects through a novel mechanism of action, combined therapy with other recently approved melanoma agents could further improve health outcomes.

Intervention: T-VEC is an oncolytic immunotherapy under development for advanced melanoma. Oncolytic immunotherapy involves using a genetically engineered virus that has been programmed to attack tumor cells directly and generate a systemic anticancer immune response. T-VEC is a genetically modified variant of herpes simplex virus type 1 from which two genes have been deleted: the genes encoding neurovirulence factors ICP34.5 and ICP47.³⁹²

Deleting ICP34.5 prevents the virus from replicating in normal, postmitotic cells; this modification purportedly results in a high degree of viral selectivity for replicating in tumor cells (which retain proliferative capability) while leaving nearby, healthy cells unharmed.^{393,394} ICP47 inhibits antigen presentation by infected cells, and deleting this factor has been shown to increase levels of major histocompatibility complex 1 on the cell surface of virally infected cells, potentially leading to improved antigen presentation.^{393,394} The virus has been modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF), which functions to recruit immune cells (i.e., dendritic cells, granulocytes, and macrophages) to the site of viral infection.³⁹⁵

T-VEC reportedly has a dual mechanism of action in treating melanoma. Its direct cytotoxic effects take place at the tumor injection site. The virus infects and replicates within tumor cells, triggering cell lysis and death (i.e., oncolytic activity). The viral particles then infect nearby tumor cells, continuing a cycle of viral replication, cell lysis, and cell death.^{393,395} Besides T-VEC's local oncolytic activity, the agent may also elicit a systemic immune response specific to tumor cells. Malignant-cell lysis exposes the immune system to a variety of tumor antigens, potentially initiating an adaptive immune response.^{395,396} GM-CSF encoded by the genetically modified virus purportedly enhances this systemic immune response by recruiting dendritic immune cells to sites of viral infection.³⁹⁵

In a phase II trial, peripheral blood and tumor samples were taken to characterize the downstream immune effects of intratumoral T-VEC therapy compared with these effects in tumors injected with GM-CSF. Patients treated with T-VEC had elevated levels of T cells specific to melanoma-associated antigen recognized by T cells (MART-1) and decreased levels of regulatory T cells, suppressor T cells, and myeloid-derived suppressive cells.³⁹⁷

In clinical trials, investigators administered an initial T-VEC injection at a concentration of 10^6 pfu/mL, with up to 4 mL total volume injected per lesion. After 3 weeks of rest, patients received biweekly followup T-VEC doses at a concentration of 10^8 pfu/mL, with up to 4 mL total volume injected per lesion.^{398,399}

Clinical trials: T-VEC is being tested in injectable stage IIIB, IIIC, or IV melanoma that is not surgically resectable. Results from the phase III OPTiM/Study (NCT00769704) were presented at the 2014 ASCO annual meeting, which evaluated durable response rates and overall survival in 436

patients with advanced melanoma.^{398,400} Investigators reported a durable response rate (primary endpoint) of 16% (95% CI, 12% to 21%) in patients who had received T-VEC versus 2% (95% CI, 0% to 5%) in patients who were treated with GM-CSF alone. Investigators also reported an increase of 4.4 months in overall survival (secondary endpoint) with T-VEC versus GM-CSF (23.3 months and 18.9 months, respectively; HR, 0.79; 95% CI, 0.62 to 1.00; p=0.051). Studies are ongoing to better understand the benefits of T-VEC in patients with melanoma as a single agent or in combination with other therapies. The most common adverse events associated with T-VEC included chills, fatigue, and pyrexia; none of the patients experienced any grade 3 or 4 adverse events.⁴⁰⁰

Manufacturer and regulatory status: T-VEC was developed by BioVex Group, Inc. (Woburn, MA), which was acquired by Amgen, Inc. (Thousand Oaks, CA), in March 2011.⁴⁰¹ A phase III trial of T-VEC in patients with advanced melanoma, the OPTiM/Study (NCT00769704), has been completed and was the basis of Amgen's July 2014 regulatory filing with FDA.⁴⁰²⁻⁴⁰⁴ In April 2015, the Cellular, Tissue and Gene Therapies Advisory Committee and the Oncologic Drugs Advisory Committee of FDA convened a joint meeting to review the biologics license application for T-VEC.⁴⁰⁵ Committee members voted 22-1 in favor of recommending approval.⁴⁰⁶ FDA's Prescription Drug User Fee Act decision date for T-VEC is October 27, 2015.⁴⁰⁷

If approved, T-VEC would be indicated for adults with stage IIIb, IIIc, or IV melanoma who have at least one lesion that is accessible for injection but who are ineligible for curative surgical resection.³⁹⁸ Patients with bone or cerebral metastases would be ineligible for T-VEC. A phase I/II trial is investigating combination therapy using T-VEC and ipilimumab in patients with treatment-naïve, advanced melanomas that are ineligible for surgical resection.⁴⁰⁸ Future indications may include T-VEC as a part of combination therapy with other recently approved therapies for advanced melanoma.

Diffusion and cost: No pricing information is available at this time for T-VEC, and little precedent exists for the pricing of oncolytic viral immunotherapy, but costs are expected to be high because T-VEC production requires complex processes to generate highly concentrated, high-purity viral material. Storing and handling this agent will require additional precautionary measures.⁴⁰⁹ Costs of other oncologic immunotherapies, such as sipuleucel-T (Provenge®) for treating prostate cancer, are between \$90,000 and \$100,000 per patient per regimen. Should ipilimumab be approved as part of combination therapy with T-VEC, treatment costs would further increase.

Because T-VEC is not yet FDA approved, no coverage, coding, or payment information is available. As an injection administered in a health care setting, T-VEC would be covered under Medicare Part B benefits. Third-party payers generally cover use of other recently approved melanoma therapies that have demonstrated efficacy (i.e., ipilimumab, vemurafenib) for their labeled indications.⁴¹⁰⁻⁴¹⁸

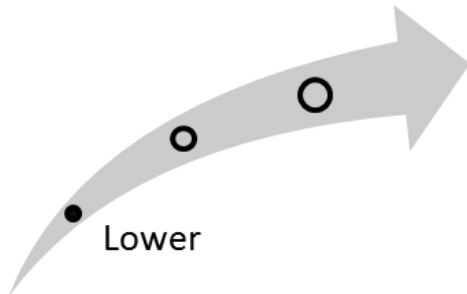
Clinical Pathway at Point of This Intervention

Patients with disseminated or unresectable or metastatic melanoma are typically treated with one of a number of systemic therapies and/or radiation therapy.⁴¹⁹ Standard systemic therapies include dacarbazine, high-dose interleukin-2, ipilimumab, temozolomide, or paclitaxel with or without cisplatin or carboplatin. For patients whose melanoma harbors an activating mutation in the gene encoding *BRAF*, therapies targeting the mitogen-activated protein (MAP) kinase pathway (e.g., dabrafenib, trametinib, vemurafenib) are also an option.

In a late-stage trial, T-VEC injections were provided as a monotherapy to patients with advanced disease and injectable lesions. However, because T-VEC has a novel mechanism of action, this agent could complement available chemo- or immunotherapies. In particular, T-VEC may be used in

combination with so-called immune checkpoint inhibitors such as the CTLA-4 inhibitor ipilimumab and PD-1 inhibitors (e.g., nivolumab, pembrolizumab). Two early phase clinical trials—testing T-VEC plus ipilimumab and T-VEC plus pembrolizumab—are ongoing.^{420,421}

Figure 12. Overall high-impact potential: talimogene laherparepvec (T-VEC) for treatment of advanced melanoma



Opinions differed among experts commenting on this intervention. Four experts thought T-VEC could address a medical need, and as a genetically engineered virus, it has potential to improve outcomes by targeting cancer through a mechanism that differs from standard therapies. They also thought that as the first oncolytic virus to show efficacy against cancer, it could lay the groundwork to develop more efficacious interventions. One expert also believes T-VEC’s potential can increase dramatically if used in combination with another immunotherapy. Meanwhile, two experts were concerned T-VEC does not have the potential to address an unmet need because of the limited clinical data and because increased overall survival was not statistically significant. Additionally, being first of its kind could also hinder T-VEC’s adoption unless safety and efficacy are clearly demonstrated in future studies. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on talimogene laherparepvec for treating advanced melanoma.⁴²²⁻⁴²⁷ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Patients with advanced melanoma have poor outcomes, and an unmet need exists for interventions that can improve their quality of life and extend their survival, all experts agreed. Most thought evidence demonstrating T-VEC’s efficacy for treating melanoma is insufficient. However, they thought T-VEC has a moderate potential to improve patient outcomes based on its novel mechanism of action, increased survival trends, and the lack of serious adverse events. Despite overall survival not reaching statistical significance, T-VEC is a potential novel option that could provide benefit if used in combination with other melanoma treatments, two experts thought.^{424,425}

Acceptance and adoption: Experts anticipated clinicians might hesitate to adopt T-VEC. For instance, physicians might be concerned about handling high titers of a live herpes virus and having insufficient data demonstrating overall survival benefits; another issue is that T-VEC is not an option for all patients. Conversely, experts thought the lack of therapeutic options and the relatively good safety profile could encourage adoption among clinicians and patients because T-VEC is a noninvasive and safe treatment that could improve outcomes, even though some patients might be reluctant to receive an intervention that is genetically engineered.

Health care delivery infrastructure and patient management: As an attenuated virus that is injected into the tumor, T-VEC will pose little to no disruption to health care delivery and patient

management, experts believe. Storage and handling will be similar to that of other virus-based vaccines, and patients eligible to receive T-VEC would have already undergone several treatments, some of which would probably have been administered as an injection. One clinician pointed out that T-VEC would pose little disruption as a single agent, but might require some additional infrastructure and training for use as a combination therapy.⁴²⁴

Health disparities: The anticipated high cost of T-VEC is expected to have a moderate impact on costs and health disparities, most experts agreed. If no insurance coverage is offered, only people with high socioeconomic status would be able to afford this therapy. Even with insurance coverage, copayments could be high and unaffordable to some patients.

Thyroid Cancer Intervention

Lenvatinib (Lenvima) and Sorafenib (Nexavar) for Treatment of Differentiated Thyroid Cancer

Unmet need: Differentiated thyroid cancer (i.e., follicular and papillary thyroid cancers) accounts for approximately 94% of thyroid cancer diagnoses.⁴²⁸ Most cases of differentiated thyroid cancer are highly treatable with surgery and radioactive iodine (RAI), and patients have an excellent prognosis. However, when thyroid cancers recur or become refractory to RAI therapy, prognosis worsens significantly. Until recently, treatment options for patients with advanced, RAI-refractory disease were limited to surgery, radiation therapy, and pharmacological suppression of thyroid-stimulating hormone. In November 2013, FDA approved the multikinase inhibitor sorafenib for treating RAI-refractory thyroid cancer.⁴²⁹ Although sorafenib has improved outcomes in this patient population, its response rate can be as low as 12%. Therefore, additional interventions are needed for patients whose disease does not respond well to sorafenib. In February 2015, FDA approved lenvatinib (LenvimaTM), another multikinase inhibitor that could provide an alternative approach for treating patients who have locally advanced or metastatic, RAI-refractory thyroid cancer.^{430,431}

Intervention: The first-line treatment for differentiated thyroid cancer usually involves surgically resecting or ablating the affected tissues combined with RAI therapy.⁴³² Although ablation with RAI is effective for differentiated thyroid cancer, the disease may become resistant and difficult to treat. Several multikinase inhibitors are under study for treating RAI-resistant thyroid cancer, and among them, FDA has approved only two— lenvatinib and sorafenib— for this indication.^{431,433}

Lenvatinib and sorafenib are oral, small-molecule drugs with broad specificity for a range of tyrosine kinases that modulate angiogenesis and tumor cell proliferation and survival.^{430,434} They target vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs), and platelet-derived growth factor receptors as well as *c-KIT* and *RET*, which are proto-oncogenes in the MAP kinase pathway.^{430,435} By binding and inhibiting the kinase activity of these molecular targets, lenvatinib and sorafenib purportedly interfere with angiogenesis and cell proliferation, processes that drive tumor growth and spread. In preclinical studies, sorafenib inhibited the growth of thyroid tumor cells harboring *BRAF*^{V600} or *RET* mutations; in vitro data also demonstrated the efficacy of lenvatinib against *RET* gene fusions, which drive cell proliferation in some differentiated thyroid cancer models and are present in a substantial number of differentiated thyroid cancers.⁴³⁵⁻⁴³⁸ Additionally, lenvatinib may counteract a mechanism of resistance to VEGFR inhibition through the drug's inhibition of FGFR, a target for which sorafenib and other approved multikinase inhibitors have little activity.⁴³⁰

In late-phase clinical trials, patients with locally advanced or metastatic, RAI-refractory differentiated thyroid cancers were treated with once daily, oral lenvatinib 24 mg, or twice daily sorafenib 400 mg (identical to the dosing established for FDA-approved sorafenib indications).⁴³⁹⁻⁴⁴¹ Sorafenib prescribing information indicates that treatment interruption or dose reduction may be required to manage dose-related toxicity or adverse events; regimens may be adjusted to 400 mg once daily or every other day.⁴³⁹

Clinical trials: Investigators have reported promising results from phase II trials of various tyrosine kinase inhibitors (e.g., axitinib, cabozantinib, lenvatinib, motesanib, pazopanib, sorafenib, sunitinib) in treating RAI-refractory thyroid cancer; however, data from randomized controlled trials have been lacking.⁴²⁸ Therefore, researchers undertook two phase III trials, SELECT and DECISION, to assess the efficacy of lenvatinib and sorafenib, respectively, compared with placebo in patients with progressive, RAI-refractory, differentiated thyroid cancer.^{440,441}

Lenvatinib. In February 2015, Schlumberger and collaborators published results from the SELECT trial in the New England Journal of Medicine. In this trial, 392 patients with RAI-

refractory differentiated thyroid cancer were randomly assigned to receive lenvatinib or placebo. Patients treated with lenvatinib had a significantly prolonged progression-free survival, as compared with placebo (18.3 months vs. 3.6 months; HR, 0.21; $p < 0.0001$). Similarly, patients in the lenvatinib group also experienced a superior response rate over the placebo group (64.8% vs. 1.5%; $p < 0.001$). At the time of the analysis, median overall survival had not been reached and the most common grade 3–4 lenvatinib-related adverse events were appetite decrease, diarrhea, fatigue, hypertension, proteinuria, and weight loss. Twenty deaths were reported in the study, six of which occurred during treatment and were considered lenvatinib-related. Because of adverse events, the initial dose of 24 mg per day was reduced in 78.5% of patients and discontinued in 14.2% of patients.⁴⁴² Additionally, patient recruitment for the postmarketing study LEN01T has begun to identify additional adverse reactions not reported previously in patients receiving lenvatinib.⁴⁴³

Sorafenib. At the 2013 ASCO annual meeting, Brose and colleagues reported that out of 417 patients, those in the sorafenib arm (400 mg, twice daily; $n = 207$) of the DECISION trial demonstrated a significant increase the primary endpoint of progression-free survival versus placebo (10.8 months vs. 5.8 months; HR, 0.58; $p < 0.0001$); these results were later published in the July issue of *Lancet*.^{444,445} No significant difference was found in overall survival, but median overall survival had not been reached at the time of primary analysis data cutoff. Seventy percent of patients in the placebo arm crossed over to sorafenib at the time of disease progression per the study protocol, which could obscure any overall survival benefit. Adverse events associated with sorafenib treatment were consistent with the known safety profile of the drug and included hand-foot skin reactions, diarrhea, alopecia, rash/desquamation, fatigue, weight loss, and hypertension.^{444,446} Two deaths during the trial—one in each study arm—were attributed to the study drug.⁴⁴⁴ Clinical benefit of sorafenib has been replicated in preliminary studies treating patients who have advanced follicular and papillary thyroid carcinomas.⁴⁴⁷

Mid-stage trials sponsored by the Memorial Sloan Kettering Cancer Center (New York, NY) are investigating combination therapy with sorafenib and everolimus or temsirolimus (mTOR inhibitors) for treating thyroid cancer.^{448,449} Additionally, the National Cancer Institute is sponsoring mid-stage trials of sorafenib in patients with medullary thyroid cancer,⁴⁵⁰ as well as in young patients (aged 2–21 years) with papillary thyroid cancer.⁴⁵¹ Additional studies of sorafenib are ongoing in several solid tumor types, including a manufacturer-sponsored, phase III study in patients with breast cancer.^{452,453}

Manufacturer and regulatory status: In February 2015, manufacturer Eisai Co., Ltd. (Tokyo, Japan), received FDA approval of its multikinase inhibitor lenvatinib for treating locally recurrent or metastatic, progressive RAI-refractory thyroid cancer. FDA had assigned priority review to the new drug application for lenvatinib in October 2014^{431,454} and had granted orphan drug designation for treating thyroid cancer in December 2012.^{455,456}

Sorafenib was developed by Bayer AG, (Leverkusen, Germany), in collaboration with Onyx Pharmaceuticals, Inc., now a subsidiary of Amgen. Basing its decision on data from the phase III DECISION trial, FDA approved sorafenib for treating RAI-refractory thyroid cancer, in November 2013.^{433,457} Furthermore, between June and July 2014, Bayer received approval for sorafenib for treating RAI-refractory thyroid cancer in Canada, the European Union, and Japan.^{458–460} Sorafenib had received FDA approval for treating advanced renal cell carcinoma in December 2005; approved indications were expanded to unresectable hepatocellular carcinoma in November 2007.^{439,461}

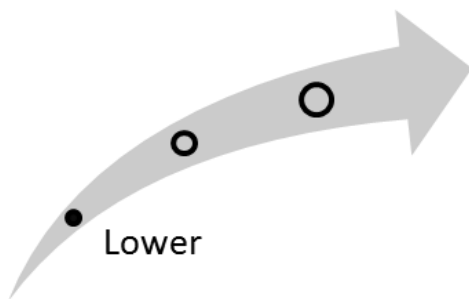
Diffusion and cost: A May 2015 query of GoodRx found a price for lenvatinib of about \$14,300 for 90 capsules of 24 mg and identified the cost for sorafenib of about \$12,600 for 120, 200 mg tablets. The prescription information of multikinase inhibitors recommend a dose of 24 mg, once daily, of lenvatinib or taking 400 mg, twice daily, of sorafenib for treating RAI-refractory thyroid cancer.^{462,463} Therefore, a monthly supply of lenvatinib and sorafenib would cost about

\$4,800 and \$12,600, respectively, per month. Due to the recency of lenvatinib's approval, coverage, coding, or payment information for lenvatinib is unavailable. However, drugs intended to treat patients in whom cancer has been diagnosed are typically covered for their FDA-approved indications. This is the case for sorafenib, because several third-party payers have established coverage policies for treating differentiated thyroid cancer. Among a group of representative, private, third-party payers that publish their coverage policies online, four had policies specific to coverage of sorafenib.⁴⁶⁴⁻⁴⁶⁷ Commercially insured patients who cannot afford copayments, Eisai offers the E.A.S.Y.TM Savings Program, which offers patients a \$0 copayment for each lenvatinib prescription.⁴⁶⁸ Similarly, Bayer offers financial-assistance options through REACH[®], a patient-assistance program for patients prescribed sorafenib.⁴⁶⁹

Clinical Pathway at Point of This Intervention

Therapy options for RAI-refractory, differentiated thyroid cancer typically include some combination of surgical resection, external beam radiation therapy, and pharmacological suppression of thyroid-stimulating hormone with thyroxine.⁴³² Several systemic therapies have been studied for treating patients who have such thyroid cancer. Unfortunately, differentiated thyroid cancer does not typically respond well to treatment with cytotoxic chemotherapy (e.g., doxorubicin). Therefore, other treatment options are being investigated for treating this patient population; options include several tyrosine kinase inhibitors, such as lenvatinib, pazopanib, sorafenib, and sunitinib. Lenvatinib and sorafenib are the only FDA-approved multikinases for treating locally recurrent or metastatic, progressive, RAI-refractory thyroid cancer.⁴⁷⁰ Another possible competitor of lenvatinib and sorafenib, sunitinib, is under examination in ongoing late-stage trials. Sunitinib is commercially available and could be prescribed off label.^{471,472}

Figure 13. Overall high-impact potential: multikinase inhibitors lenvatinib (Lenvima) and sorafenib (Nexavar) for treatment of differentiated thyroid cancer



Although they do not provide a cure, lenvatinib and sorafenib are capable of partially treating and stabilizing RAI-refractory thyroid cancer, as demonstrated by clinical results, opined some experts. Basing their opinions on improved progression-free survival data, most considered lenvatinib and sorafenib to have potential to improve outcomes in patients. A head-to-head comparison between the two drugs has not been performed, the experts noted; such studies could help determine which agent would benefit patients more. Another expert also noted that lenvatinib treatment was associated with a high incidence of adverse events, which during the trial caused clinicians to lower patient doses or prematurely discontinue treatment. The magnitude of the drugs' impact is lessened by the relatively small number of patients who would be eligible for the treatment and the oral administration route, which reduces any potential impact on health care staffing or infrastructure. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of lenvatinib for treating differentiated thyroid cancer,⁴⁷³⁻⁴⁷⁸ and six experts, with similar backgrounds, offered perspectives on the topic of sorafenib for treating differentiated thyroid cancer.⁴⁷⁹⁻⁴⁸⁴ Of these experts, a clinician commented on both interventions.^{476,481} We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need in differentiated thyroid cancer purportedly addressed by lenvatinib and sorafenib was seen by experts as having moderate importance, which could be limited by the relatively small patient population affected. Lenvatinib could be a potential alternative for patients who do not respond to sorafenib to address the unmet need, most of the experts thought. Although they noted increased side effects and uncertainty about lenvatinib treatment duration, three experts considered the difference in progression-free survival to be impactful.^{473,474,477} Sorafenib was shown to improve progression-free survival, as compared with placebo, and the disease was stabilized or partially treated in 70% to 80% patients. Basing their opinions on sorafenib's clinical performance, experts concluded it could become standard of care for this patient population (although not all patients' disease responds).

Acceptance and adoption: Lenvatinib has moderate potential to be adopted by patients and clinicians for treating RAI-refractory thyroid cancer, experts opined, due to limited treatment options and its oral administration and improved efficacy. However, four experts also thought the added adverse events could be a barrier to acceptance.^{473-475,478} An expert also noted adoption of lenvatinib could be decreased because it would have to compete with sorafenib,⁴⁷³ for which experts anticipated moderate-to-wide physician and patient acceptance. Experts noted that as an oral medication, sorafenib should easily diffuse, especially because it is already approved and covered by insurance. A clinical expert suggested sorafenib could eventually be used as first-line treatment in addition to second-line treatment.⁴⁸³

Health system infrastructure and patient management: Because it is an oral drug taken at home, lenvatinib is not likely to disrupt health care delivery or patient management, the experts thought. For sorafenib, the experts noted that oncologists have been prescribing it for a few years and disruption to health care infrastructure and patient management has been minimal. An expert noted that taking sorafenib orally led to a slight change in patient management because the treatment is taken at home instead of at a clinic. This shift then leads to patients having to visit hospitals to monitor disease progression and onset of adverse events.⁴⁸⁴

Health disparities: Most experts thought that despite being an expensive drug, sorafenib has limited potential to affect health disparities, because reimbursement is available from insurance and the manufacturer's REACH program, which makes the drug available to patients without health insurance. Lenvatinib costs less than sorafenib, but is still expensive and would also be reimbursed by third-party payers; therefore, disparities would be experienced by patients who do not have health insurance or cannot afford drug copayments.^{473,475,478} However, two experts expect the effect to be lessened because of the small patient population.^{481,484} Additionally, if lenvatinib and sorafenib continue to show efficacy in additional trials, more insurance carriers may offer coverage.

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