

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

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## **Priority Area 02: Cancer**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

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**Prepared by:**

ECRI Institute  
5200 Butler Pike  
Plymouth Meeting, PA 19462

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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 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](mailto:effectivehealthcare@ahrq.hhs.gov).

Richard Kronick, Ph.D.  
Director  
Agency for Healthcare Research and Quality

David Meyers, M.D.  
Acting Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

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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 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 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 150 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 31 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 November 4, 2014, in this priority area; *and* (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (A total of 201 topics in this priority area were being tracked in the system as of November 4, 2014.) 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 within that disease state. We present 13 summaries on 18 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	Moderately high
2. Anastrozole (Arimidex) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	No high-impact potential; archived on basis of experts’ comments
3. Ceritinib (Zykadia) for treatment of nonsmall cell lung cancer	No high-impact potential; archived on basis of experts’ comments
4. Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Prior high-impact topic (June 2014); archived because it no longer meets criteria for tracking; FDA approved more than 2 years ago
5. Everolimus (Afinitor) for treatment of advanced estrogen receptor–positive breast cancer	Prior high-impact topic (June 2014); archived because it no longer meets criteria for tracking; FDA approved more than 2 years ago
6. Exemestane (Aromasin) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	No high-impact potential; topic archived on basis of experts’ comments
7. *Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High

Topics	High-Impact Potential
8. *Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma	High
9. *Idelalisib (Zydelig) for treatment of chronic or small lymphocytic leukemia	High
10. *Idelalisib (Zydelig) for treatment of indolent non-Hodgkin's lymphoma	High
11. Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Prior high-impact topic (June 2014); archived because manufacturer is no longer pursuing indication for hepatocellular carcinoma
12. Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Prior high-impact topic (June 2014); archived because manufacturer is no longer pursuing indication for pancreatic cancer
13. *Lenvatinib for treatment of differentiated thyroid cancer	Lower end of the high-impact-potential range
14. Liposome encapsulated irinotecan (MM-398) for treatment of pancreatic cancer	No high-impact potential; archived on basis of experts' comments
15. Magnetic resonance imaging–ultrasound image fusion to guide prostate biopsy	Prior high-impact topic (June 2014); archived because it no longer meets criteria for tracking; FDA approved more than 2 years ago
16. MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy	Prior high-impact topic (June 2014 and previous high impact reports); archived because after nearly 2 years on market, adoption has been extremely low and no additional evidence of benefit has become available.
17. Methylated Septin 9 blood test for colorectal cancer screening	No high-impact potential at this time
18. *Nivolumab (Opdivo) for treatment of advanced melanoma	Moderately high
19. *Ovarian tissue cryopreservation for fertility preservation in females undergoing gonadotoxic cancer therapy	Lower end of the high-impact-potential range
20. *Palbociclib (Ibrance) for treatment of estrogen receptor–positive breast cancer	Moderately high
21. Panobinostat for treatment of recurrent multiple myeloma	No high-impact potential; archived on basis of expert comments
22. *Pembrolizumab (Keytruda) for treatment of advanced melanoma	Moderately high
23. *Radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases	Moderately high
24. *Ramucirumab (Cyramza) for treatment of gastric cancer	Lower end of the high-impact-potential range
25. Ramucirumab (Cyramza) for treatment of metastatic nonsmall cell lung cancer	No high-impact potential; archived on basis of expert comments
26. *Ruxolitinib (Jakafi) for treatment of polycythemia vera	Lower end of the high-impact-potential range
27. *Siltuximab (Sylvant) for treatment of multicentric Castleman's disease	Lower end of the high-impact-potential range
28. *Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	Lower end of the high-impact-potential range
29. *Specialized care model for adolescents and young adults with cancer	Moderately high
30. *Stool DNA molecular test (Cologuard) for colorectal cancer screening	Lower end of the high-impact-potential range
31. *Talinogene laherparepvec (T-VEC) for treatment of advanced melanoma	Lower end of the high-impact-potential range

FDA: U.S. Food and Drug Administration



## Discussion

### Prior Potential High Impact Topics Archived

The following five topics that were topics with high-impact potential in previous reports have been archived since the June 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 U.S. Food and Drug Administration [FDA] approval), their manufacturers are no longer pursuing clinical development for the indication that was being tracked, or they have not been adopted as anticipated.

- **Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer:** In the June 2014 High-Impact Interventions report (and earlier high-impact reports), commenters suggested that enzalutamide had significant potential to improve health outcomes in patients with castration-resistant prostate cancer (CRPC), citing the positive results in terms of progression-free and overall survival observed in two randomized controlled trials. FDA approved pertuzumab in August 2012. This drug has been diffusing for more than 2 years; therefore, it no longer meets criteria for tracking and has been archived in the horizon scanning system.
- **Everolimus (Afinitor) for treatment of advanced estrogen receptor–positive breast cancer:** In the June 2014 report (and earlier high-impact reports), commenters thought this drug had moderate high-impact potential and suggested that results for progression-free survival in endocrine therapy–resistant, metastatic breast cancer were promising for a condition with few treatment options. FDA approved everolimus for treating breast cancer in July 2012. This drug has been diffusing for more than 2 years; therefore, it no longer meets criteria for tracking and has been archived in the horizon scanning system.
- **Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma and pancreatic cancer:** In the June 2014 report (and earlier high-impact reports), commenters considered irreversible electroporation to be in the lower end of the high-impact-potential range and viewed it as a potentially important addition to cancer treatment options. They thought it could be useful for treating pancreatic cancer, for which commenters noted a large unmet need, and might shift the way patients are managed. On the other hand, for hepatocellular cancer, the limited evidence on irreversible electroporation does not appear to offer advantages over other options, the commenters stated. They concurred irreversible electroporation could be the only option for patients with cancer localized near critical structures or organs. We archived this topic because the manufacturer appears to have changed its focus for development from liver and pancreatic cancers to prostate cancer treatment, and we found no evidence of continued development (i.e., ongoing clinical trials) for treating liver and pancreatic cancer.
- **MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy:** Breast-conserving surgery (lumpectomy) followed by radiation therapy for early stage breast cancer has been shown to achieve low recurrence rates equivalent to those achieved with total mastectomy. Achieving optimal outcomes requires that the excised tumor’s tissue margins be free of cancer. If subsequent pathologic analysis reveals that tissue margins are not cancer free, patients typically need to undergo a second surgery to remove additional tissue, and this occurs in about 25% of cases. The MarginProbe™ System (Dune Medical Devices, Caesarea, Israel) purportedly provides an objective means of rapidly assessing surgical margins intraoperatively using radiofrequency (RF) spectroscopy during lumpectomy. In January 2013, FDA approved the MarginProbe

device for marketing, but since then, adoption has been extremely low because of limited evidence of benefit and lack of payer reimbursement. The system cost, as reported to ECRI Institute's PricePaid database by hospitals acquiring the device, is about \$40,000. Experts commenting on MarginProbe thought it has potential to improve patient quality of life and outcomes by avoiding a need for second surgeries in women undergoing breast-conservation surgery. However, they wanted more data determining accurate distinction between negative and positive margins to adequately evaluate the potential impact of intervention. Available data indicate that second surgeries might be reduced by six percentage points (from 25% to 19%) but the technology does not obviate the need for second surgeries. No further data have become available, and that fact along with the lack of diffusion led to a decision to archive this topic.

- **Magnetic resonance imaging–ultrasound image fusion to guide prostate biopsy:** In the June 2014 report (and earlier high-impact reports), commenters indicated that substantial shortcomings exist in prostate biopsy methods and that magnetic resonance imaging–transrectal ultrasound (MRI-TRUS) fusion has potential to improve the detection rate of clinically significant prostate cancer. MRI-TRUS was considered to have high-impact-potential in the lower end of the range of high impact. This topic has been archived because it has been FDA-cleared and its diffusion has been tracked for more than 2 years in the horizon scanning system, so it no longer meets criteria for tracking.

## Eligible Topics Not Deemed High Impact

In this section, we briefly discuss topics in the table above that were deemed to have no high-impact potential at this time based on reviews made by experts commenting, poor outcomes in clinical trials, or no longer meeting Healthcare Horizon Scanning System requirements.

- **Aromatase inhibitors; anastrozole (Arimidex) and exemestane (Aromasin) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer:** Anastrozole and exemestane are new drugs that have potential to decrease the risk of developing breast cancer in women at high risk, commenters thought. However, they noted that efficacy was not dramatically better than other available drugs purported to decrease risk of breast cancer, and they thought patients would require constant monitoring for medication-associated musculoskeletal and endometrial issues. Because these medications are taken orally, commenters did not anticipate many barriers for their acceptance by patients and physicians but thought it might be challenging for patients to follow a daily regimen for several years. Phase III trials have been completed and no new trials have been registered. Generic versions of aromatase inhibitors are available for patients, and these may be used off label for this indication. Both topics were archived on the basis of expert comments indicating that if these drugs represented improvement over existing options, the improvement was incremental at best.
- **Ceritinib (Zykadia) for treatment of nonsmall cell lung cancer:** Another previously FDA-approved drug, crizotinib (Xalkori<sup>TM</sup>), has shown efficacy for patients with the anaplastic lymphoma kinase (ALK) gene rearrangement, but a high rate of ALK-mutated cancers develop resistance to it, which leaves patients with limited options. Ceritinib is a second-generation targeted therapy that was developed to address this need. Data from only a single clinical trial are available; most commenters considered the improved progression-free survival and response rate to be better than first-line treatment and considered ceritinib to have moderate potential to improve patient health. However, a clinical commenter noted two factors limiting use of this ALK inhibitor: its cost is higher than the \$120,000-per-year

cost of crizotinib and the incidence of serious adverse events is higher than that of crizotinib. The commenter noted that this has resulted in a very high discontinuation rate by patients prescribed this medication. Experts opined that followup studies are needed to better assess the safety and efficacy of ceritinib. Ceritinib was FDA approved in April 2014; as a second-generation ALK inhibitor, ceritinib would not dramatically change patient management or health care infrastructure, the experts thought. For all of these reasons this topic was archived.

- **Liposome-encapsulated irinotecan (MM-398) for treatment of pancreatic cancer:** Overall, commenters thought any intervention with potential to improve outcomes in patients with pancreatic cancer has high-impact potential, because of this disease's rapid progression and late-stage diagnosis in most cases. However, most commenters considered the 2-month overall survival increase to be a marginal improvement. Additionally, one clinician commenter thought a better approach to assess the efficacy of liposome-encapsulated irinotecan would have been to compare it with free irinotecan instead of 5-fluorouracil, as was studied in trials. Commenters did not anticipate barriers for adoption by clinicians and patients, and liposome-encapsulated irinotecan was not seen as having potential to affect health disparities or the way patients are managed. Liposome-encapsulated irinotecan was expected to be expensive, and the patient population using it was expected to be small, so commenters thought third-party payers would likely offer coverage upon FDA approval. In December 2014, FDA granted breakthrough therapy status to liposome-encapsulated irinotecan. On the basis of the marginal health improvement and a lack of additional ongoing clinical trials to further test efficacy and safety, this topic was thought to have no potential for high impact and was archived.
- **Methylated Septin 9 blood test for colorectal cancer screening:** As a blood-based screening method for colorectal cancer (CRC), this test had been designated in December 2013 as a potential high-impact intervention; but new expert comments based on more recent data deemed the test's specificity and sensitivity to be low, relative to other screening methods. Commenters saw little potential at this time, although they thought the test might have potential to improve CRC screening rates in patients who prefer a blood test over a stool test. In June 2014, FDA released a "not approvable letter" in which it requested from the company additional data on the likelihood of adoption by individuals who are not compliant with screening recommendations. The topic will be tracked in the horizon scanning system until these data become available.
- **Panobinostat for treatment of recurrent multiple myeloma:** Clinical data showed that panobinostat has minimal potential to address an unmet need, commenters thought. This intervention is associated with substantial toxicity, which led to treatment discontinuation by more than a third of patients. On the other hand, patients with bortezomib-refractory multiple myeloma have few treatment options; thus, commenters thought the small improvement observed might lead physicians to offer it as an option for relapsed/refractory multiple myeloma. However, commenters did not think the risks of taking panobinostat outweighed its benefits. Additionally, FDA's Oncologic Drugs Advisory Committee voted 5-2 against accelerated approval of panobinostat in November 2014. Therefore, we archived the topic.
- **Ramucirumab (Cyramza) for treatment of metastatic nonsmall cell lung cancer:** Commenters indicated that ramucirumab has small potential to address an unmet need and unanimously agreed it would be difficult to justify exposing patients to additional adverse events to extend life by only several weeks as reported in clinical trials. In particular, one

commenter with a clinical perspective did not consider ramucirumab to be an advancement for treating nonsmall cell lung cancer (NSCLC), suggesting a certain subgroup of patients might benefit from ramucirumab but that predictive biomarkers for such a patient population have not been identified. Two commenters opined that ramucirumab might improve outcomes for a subpopulation, but this would need to be explored in future clinical trials; however, no additional phase III trials were registered in the National Clinical Trials database, so such data do not appear to be forthcoming. In December 2014, basing its decision on the results of the phase III REVEL trial, FDA approved ramucirumab in combination with docetaxel for treating patients with metastatic NSCLC whose disease 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 ALK and disease that has progressed after targeted therapy. This topic was archived on the basis of experts' comments citing marginal efficacy and lack of additional phase III trials that could provide more data on outcomes.

## **Eligible Topics Deemed High Impact**

Topics that emerged as having potential for high impact in the cancer area include novel drugs, biologics, and devices for treatment; novel screening and diagnostic tests; a device used during surgical procedures; a specialized care delivery program for adolescents and young adult oncology patients; and a procedure intended to preserve fertility in female cancer patients. The conditions that these interventions address include both solid tumors (advanced melanoma, breast cancer, CRC, gastric cancer, prostate cancer, and thyroid cancer) and hematologic malignancies (Castleman's disease, chronic lymphocytic leukemia (CLL), mantle cell lymphoma, non-Hodgkin's lymphoma, and polycythemia vera). The group of therapeutic agents includes both small-molecule and biologic drugs. Most small-molecule drugs have a well-defined mechanism of action and target a specific signaling pathway. Large-molecule drugs include an antibody-drug conjugate (ADC) and four monoclonal antibodies. The ADC targets a tumor-associated antigen overexpressed by a subset of cancers and represents a personalized therapy intended for a specific patient population. The monoclonal antibodies target molecules involved in two hallmarks of cancer: angiogenesis and immune tolerance. 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. Diagnostic interventions offer potentially simpler or purportedly improved solutions to existing technologies.

## **Adolescent and Young Adult Oncology**

### **Specialized Care Model for Adolescents and Young Adults With Cancer**

- **Key Facts:** The improved health outcomes resulting from recent advancements in treating pediatric and older adult cancers have not been realized by adolescent and young adult (AYA) patients (aged 13–30 years). Several reasons have been given for this. AYAs represent a distinct patient population with unique clinical and supportive care needs, but many receive care on pediatric or adult hospital units where they have little in common with those patient groups in clinical concerns and issues, and psychological, emotional, educational, and financial needs. Often, treatment adherence can pose a problem in the AYA population because of life circumstances (e.g., school, lack of experience navigating the health system, limited financial resources, desire to maintain independence, concerns about appearance, concerns about maintaining peer relationships).

The National Cancer Policy Forum held a workshop in November 2013 sponsored by Livestrong foundation and the Institute of Medicine; the group published proceedings from that workshop in January 2014 outlining the needs of this special patient population.

In recognition of the unique needs of AYAs, along with the observation that pediatric cancer outcomes improved after pediatric-specific oncology care models were adopted decades ago, institutions have begun to develop specialized AYA cancer care programs. Many models have been developed; we describe one of them to illustrate how this unmet need is being addressed. Teenage Cancer Trust of the United Kingdom and the U.S.-based Teen Cancer America are two nonprofit organizations that work in partnership with hospitals in the United Kingdom and United States to develop fully dedicated AYA oncology units with tailored clinical and social space. Specially trained staff include doctors, nurses, and other support staff who specialize in common AYA cancers and care issues and who also have extensive knowledge of clinical trial opportunities for AYAs. Primary goals of these programs include improving treatment adherence; improving patient satisfaction, health outcomes, and quality of life; and achieving higher enrollment rates in clinical trials to enable robust testing of new therapies in the AYA population. For example, AYA units may offer modified schedules for treatment (e.g., late afternoon and evening) to prevent excess disruption to the daily educational and social schedules of AYA patients and to promote treatment adherence. Clinical spaces are designed to mimic a home environment with dedicated space for education and peer social activities. Family and psychosocial therapy are often provided. Additionally, the units offer youth support coordinators who are trained to address the psychosocial and supportive care needs that arise during treatment and help to ease patients' transition back into school or work. Efforts are ongoing to establish metrics to assess the health impact of these dedicated units and specialized programs. The ongoing BRIGHTLIGHT study is assessing this care model's impact on health outcomes. Development of many other AYA programs not affiliated with these organizations is also ongoing; the Lance Armstrong Foundation is providing seed funding for some AYA cancer centers. More than 30 AYA cancer programs have been established in the United States to date.

- **Key Expert Comments:** Most experts commenting on AYA oncology care model programs agreed that an important unmet medical need exists for health care models focusing on AYAs. However they expressed concerns about not having data yet to demonstrate improved health outcomes in AYAs treated under such program regimens. One clinician in particular was concerned that this care model might lead to significant structural and administrative changes, as well as associated costs, before evidence demonstrates that health outcomes could be improved. If this specialized care model is implemented, clinicians and patients would widely accept its programs, experts thought. Differences existed in expert opinions on the impact this intervention would have on health disparities: some experts thought limited access because of geographic locations of AYA cancer center programs would increase disparities while others thought the programs could decrease disparities between AYAs and non-AYAs. Cost information about these models is not readily available. Costs incurred would include medical staff and social worker trained to care for AYAs, physical environments attuned to needs of AYAs, AYA-focused support groups, extended hours, and care coordination targeted at the mobile lifestyles of many AYAs (e.g., attending college).
- **High-Impact Potential:** Moderately high

## Breast Cancer

### Ado-Trastuzumab Emtansine (Kadcyla) Antibody-Drug Conjugate for Treatment of Advanced HER2-Positive Breast Cancer

- **Key Facts:** HER2-positive breast cancer is a subclass of invasive breast cancer characterized by expression of high levels of the epidermal growth factor receptor (EGFR), HER2. This breast cancer subtype comprises about 20% of breast cancer cases and has been associated with more aggressive disease and poorer outcomes. Although treatment of HER2-positive breast cancer improved with the availability of HER2-targeted therapies such as trastuzumab (Herceptin®), lapatinib (Tykerb®), and pertuzumab (Perjeta®), many patients' cancers still progress despite treatment, and additional options are needed. Ado-trastuzumab emtansine (Kadcyla®, F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is a novel HER2-directed therapy recently approved by FDA. The drug is administered as an intravenous (IV) infusion in outpatient infusion centers. Formerly known as trastuzumab-DM1, ado-trastuzumab emtansine couples the potent chemotherapeutic agent emtansine (a microtubule assembly inhibitor) to the HER2-specific antibody trastuzumab. The toxin and antibody are coupled in such a way that emtansine is held in a stable, inactive form outside the cell, and only upon cellular uptake of the drug conjugate, mediated by antibody binding to the HER2 receptor, is emtansine released and activated. In this way, its cytotoxic activity is targeted to cells expressing HER2, potentially reducing toxicity in noncancerous tissues. Ado-trastuzumab emtansine is being studied in several phase III trials for treating HER2-positive breast cancer. Verma et al. (2012) published results from one of these trials (EMILIA), which compared the drug with second-line therapy of lapatinib and capecitabine. Results indicated that ado-trastuzumab emtansine increased progression-free and overall survival and reduced severe adverse events.

In February 2013, basing its decision on these results, FDA approved ado-trastuzumab emtansine monotherapy as second-line treatment of HER2-positive metastatic breast cancer. The biologic is given at a dosage of 3.6 mg/kg, administered by IV infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The drug is provided in 100 mg vials. A U.S.-based, online aggregator of prescription-drug prices listed costs ranging from about \$2,800 to \$3,000 per 100 mg vial. This pricing requires use of a discount coupon. Thus, a 70 kg (154 lb) person would require about 252 mg, or 2.5 vials at a cost of about \$7,500 per infusion cycle (assuming partial vials are not discarded; if partial vials cannot be reused, then the cost would be higher). Ado-trastuzumab emtansine is typically covered for labeled indications by third-party payers as a specialty pharmaceutical that requires preauthorization for outpatient infusion therapy.

- **Key Expert Comments:** Overall, experts commenting on this intervention believe that ado-trastuzumab emtansine has 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. Experts also thought 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, experts noted. They added that its cost was comparable to monthly costs of other targeted cancer therapies.
- **High-Impact Potential:** Moderately high

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

- **Key Facts:** In 2014, the American Cancer Society estimated that about 75% of the 230,000 cases of invasive breast cancer that would be diagnosed in the United States would correspond to the estrogen receptor–positive (ER+) subclass. 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+ 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 cyclin-dependent kinases (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 (Pfizer, Inc., New York, NY) selectively inhibits CDK 4 and 6 and purportedly reduces drug resistance by blocking cell-cycle progression and inhibiting cancer cell proliferation. FDA has granted palbociclib breakthrough therapy status; the drug is not yet approved. Palbociclib is administered orally daily, for 3 of 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+ breast cancer.

Finn et al. (2014) reported results from the phase II PALOMA-1 trial that compared palbociclib plus letrozole combination with letrozole alone in postmenopausal women with advanced ER+ breast cancer, which demonstrated that palbociclib increased progression-free survival and had an improved trend in overall survival. The most common adverse events associated 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 status 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. Because it has not been FDA-approved, cost or coverage information is unavailable for palbociclib. However, if approved, it is likely to be categorized as a specialty pharmaceutical and priced similarly to other cancer interventions (typically \$8,000 to \$10,000 per patient per month) and require prior authorization for coverage. Two other CDK4/6 inhibitors—abemaciclib (Eli Lilly and Co., Indianapolis, IN) and LEE011 (Novartis International AG, Basel, Switzerland)—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+ breast cancer survive long enough to develop recurrence and have limited second-line options. Therefore, they believe palbociclib has moderately high potential to improve outcomes for these patients by decreasing the drug-resistance rate; 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 also thought insurers would cover it if FDA approves the drug, which could decrease health disparities by offering an option for this patient population.

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

## Colorectal Cancer

### Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

- **Key Facts:** New screening methodologies 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 colorectal cancer 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 (NCD) for Cologuard, which indicates use of the test once every 3 years would be covered for beneficiaries. Retail cost of the Cologuard test has been reported as \$600.

- **Key Expert Comments:** Overall, experts suggested that stool DNA testing has potential to improve on the accuracy of current noninvasive stool-based tests such as fecal occult blood testing and FIT. However, the biggest shifts in patient outcomes and management were envisioned in patients switching from colonoscopy to stool DNA testing or in patients who previously would not undergo screening opting to undergo stool DNA testing, noted experts. However, other experts commenting questioned whether these changes were likely. Note: These comments were received in May 2014, before FDA approval and CMS coverage; thus we will seek additional comments to determine if expert views have changed for the next report.
- **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 Women 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 who might wish to conceive at some point in their lives after completing cancer treatment. Cryopreserved eggs or embryos obtained before treatment for later in vitro fertilization have been the only standard options not considered to be experimental. 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 30 successful pregnancies in individuals who have undergone ovarian cryopreservation and subsequent ovarian tissue transplantation. High costs are anticipated for this specialized procedure, and it is unclear whether payers would provide coverage.

An economic evaluation of fertility preservation treatments determined the procedure for cryopreserving ovarian tissue would cost approximately \$27,000. The estimated fees published online from a fertility clinic 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 preparation of 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 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 VEGF pathways, and blocking this receptor could lead to improved outcomes in patients with advanced gastric cancer. In studying ramucirumab (Cyramza<sup>®</sup>, ImClone Systems, a subsidiary of Eli Lilly and Co., Indianapolis, IN), 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 of 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 toxicity limits further treatment. Thus, an adult of about 70 kg (154 lb) would require would require about 560 mg. A June 2014 query of a U.S.-based, online aggregator of prescription-drug prices showed costs of six vials of Cyramza 100 mg/10 mL of about \$6,500 to \$7,000—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 an unmet need exists for second-line therapy for advanced gastric cancer therapies, because no FDA-approved option had been available before this approval. Although ramucirumab showed efficacy in patients with advanced gastric cancer, experts thought it has only moderate potential to fulfill this need because survival was only marginally increased and because the benefits might not outweigh the increase in adverse events. However, no other FDA-approved second-line treatments are available, and experts thought this would be accepted as a treatment option by both patients and clinicians.

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

## Hematologic Malignancies

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

- **Key Facts:** B-cell non-Hodgkin's lymphomas (NHLs), such as CLL and mantle cell lymphoma, often respond well to first-line therapy; however, most affected patients experience recurrence. In this situation, available therapies have limited or no 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. In single-arm, phase II studies reported in 2013 by Farooqui et al. and Byrd et al., ibrutinib demonstrated substantial activity in patients with mantle cell lymphoma or CLL, with response rates between 66% and 71%. More recently, data were reported by Byrd and co-authors (2014) from a randomized controlled trial of ibrutinib versus the CD20 antibody ofatumumab for treating patients with relapsed/refractory CLL. Ibrutinib significantly improved overall survival compared with ofatumumab (hazard ratio, 0.434; 95% confidence interval, 0.238 to 0.789;  $p=0.0049$ ).

FDA granted ibrutinib accelerated approval in November 2013 for treating patients with mantle cell lymphoma and in February 2014 for treating patients with CLL. In July 2014, FDA granted ibrutinib full approval for treating patients with CLL. The labeled dosage for mantle cell lymphoma is 560 mg, once daily, and for CLL, 420 mg, once daily. The retail prices for ibrutinib at the mantle cell lymphoma and CLL doses are about \$11,800 and \$8,800 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 relapsed/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). In results of a single-arm trial of idelalisib for treating relapsed/refractory indolent NHL reported by Gopal et al. (2014), a response rate of 57% was observed.

In July 2014, FDA approved idelalisib for treating relapsed/refractory CLL in combination with rituximab and for two forms of relapsed/refractory indolent NHL (follicular lymphoma and small lymphocytic lymphoma) as a monotherapy. GoodRx listed an average retail price of \$3,773 for thirty 150-mg idelalisib tablets. At a recommended dose of 150 mg twice daily, this represents a cost of approximately \$7,500 per month.

- **Key Expert Comments:** Overall, experts opined that a significant need exists for better and 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, expert commenters suggested that further confirmatory studies are needed, particularly studies comparing ibrutinib and idelalisib to alternatives. Experts noted the relatively benign side-effect profiles of ibrutinib and idelalisib and their potential to be used 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. No treatments for the disease are 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. 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 to 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 \$112,000 (or \$9,330 per month).

- Key Expert Comments:** Overall, experts 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. 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 November 2014 query of a U.S.-based, online aggregator of prescription-drug prices 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 the potential to fill a significant unmet need of patients with multicentric Castleman’s disease, given that no other FDA-approved therapies exist for this indication and basing their opinions on the promising results regarding disease response rate from the randomized clinical trial. However, siltuximab’s overall impact was limited by the small size of the eligible patient population and the preliminary nature of the data on a therapy that could potentially be taken for extended periods of time.
- **High-Impact Potential:** Lower end of the high-impact-potential range

## Prostate Cancer

### Radium-223 Dichloride (Xofigo) for Treatment of Solid-Tumor Bone Metastases

- **Key Facts:** Many solid tumors, in particular breast, prostate, and lung cancer, metastasize to bone, causing chronic pain and skeletal-related events (e.g., fractures) that adversely affect patient quality of life and survival. Among the treatment options for bone metastases are radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases. Preferential accumulation of the radioactive compound purportedly concentrates the radiation dose at the target bone metastases. Although available radionuclides have shown efficacy in palliating bone pain, the type of radiation that they emit penetrates tissues deeply enough to damage bone marrow, which limits the deliverable dose and restricts their use to one of symptom palliation. Radium-223 dichloride (Xofigo<sup>®</sup>, Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany) is a novel bone metastasis–targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than radiation generated by available radiopharmaceuticals. This treatment may reduce the side-effect profile of treatment and more effectively target bone metastases. Results reported by the developers from a double-blind, randomized controlled trial of 921 patients with metastatic castration-resistant prostate cancer (mCRPC) and skeletal metastases who were ineligible for treatment with docetaxel (Parker et al., 2013) indicated increased overall survival of 3.6 months in patients treated with radium-223 dichloride compared with survival of patients treated with placebo. An independent committee recommended that the trial be stopped early because of the positive results. Investigators reported that besides improving overall survival, treatment with radium-223 dichloride improved secondary endpoints such as the time to first skeletal-related event, percentage of patients achieving normalized total alkaline phosphatase levels, and time to biochemical disease progression. Side effects were reported as being relatively benign, suggesting that it could potentially be used in combination with other prostate cancer treatments.

After priority review, FDA approved radium-223 dichloride for treating bone metastases in patients with mCRPC in May 2013; the approval came 3 months ahead of the anticipated decision date. Bayer initiated a phase III trial to collect additional long-term safety data, and an early phase trial is examining the agent in combination with docetaxel for treating CRPC bone metastases. This agent is also under investigation for treating osteosarcoma and breast cancer with bone metastases. Radium-223 dichloride is administered intravenously at a dose of 50 kilobecquerel (1.35 microcurie)/kg, once every 4 weeks, for up to six treatment cycles. Radium-223 dichloride's reported cost is \$69,000 for a complete cycle of treatment. Third-party payers generally require preauthorization, and for Medicare beneficiaries, if authorization is granted, the treatment is covered under Part B benefits.

- **Key Expert Comments:** Experts commenting on this topic thought that radium-223 dichloride has significant potential to improve current treatments for bone metastases, particularly for patients with prostate cancer. Although experts thought radium-223 dichloride would likely be widely adopted for this indication, they thought it has similarities to other existing treatments that would limit its impact on health care system infrastructure and practices.
- **High-Impact Potential:** Moderately high

## 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®, Bristol-Myers Squibb, New York, NY) and pembrolizumab (Keytruda®, Merck & Co., Inc., Whitehouse Station, NJ), as treatment for advanced melanoma. The drug class is also under study for nonsmall cell lung cancer, gastric cancer, blood cancers, and cancers of the breast, head and neck, and urothelial tract. In results from a 135-patient, placebo-controlled trial, the highest response rate was observed in 52% of patients with advanced melanoma who were treated with 10 mg/kg of pembrolizumab 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 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, 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. (2014) 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, as compared with dacarbazine. The most common nivolumab-related adverse events were fatigue, pruritus, and nausea.

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, pembrolizumab was approved for treating ipilimumab-resistant metastatic melanoma. Although no U.S. pricing information for nivolumab is available, the Asian market price is about \$1,460 for a 20 mg vial. Pembrolizumab's cost, according to an online aggregator of prescription-drug prices, is about \$7,100 for three 50 mg vials. An expanded-access program is available. Pembrolizumab is listed on many third-party payers' formularies as a specialty pharmaceutical requiring prior authorization for use.

- **Key Expert Comments:** Nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma patients, 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 ipilimumab treatment. 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, Amgen Inc., Thousand Oaks, CA) is a herpes virus bioengineered to no longer express the neurovirulence genes ICP34.5 and ICP47. Deletion of 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, stage IIIC, or stage 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 received 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 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. Similar to 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. Four 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. Meanwhile, two experts were concerned 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. Additionally, being first of its kind could also 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: Sorafenib (Nexavar) and Lenvatinib (E7080) 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, sorafenib (Nexavar®) and lenvatinib. These tyrosine kinase inhibitors have activity against multiple kinases, including vascular endothelial growth factor receptor (VEGFR) 2, VEGFR3, RET, and BRAF. The tyrosine kinases targeted by these inhibitors purportedly regulate multiple cellular processes related to tumor growth and angiogenesis; therefore, inhibiting these kinases may be of clinical benefit to patients. Specifically, the activity of sorafenib and lenvatinib against RET may be of particular importance in treating thyroid cancer, because RET has been observed in differentiated thyroid cancers. In addition to RET, BRAF is also a sorafenib target, suggesting that activating mutations in these kinases may play a role in the pathogenesis of the disease. Sorafenib and lenvatinib 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 (2014) demonstrated an improvement in progression-free survival in patients treated with lenvatinib, as compared with placebo (18.3 months vs. 3.6 months). Similarly, Brose and colleagues (2013) also reported that sorafenib extended progression-free survival by 86% (10.8 months vs. 5.8 months for placebo).

Based on the above data, NDAs for sorafenib and lenvatinib were submitted to FDA. Lenvatinib received priority review with a decision expected by April 2015. FDA approved sorafenib in November 2013 for treating radioactive iodine–refractory thyroid cancer after a priority review. It is 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 this indication.



Several third-party payers already had policies in place that consider it medically necessary for treating thyroid cancer. Coverage is anticipated to continue to expand in the wake of the FDA approval. The retail cost for sorafenib at a dose of 400 mg twice daily is about \$11,600 per month. Sorafenib use 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 REACH<sup>®</sup>, a patient-assistance program for patients prescribed sorafenib. No cost information is available for lenvatinib but its cost is likely to be similar to sorafenib.

- **Key Expert Comments:** Although sorafenib and lenvatinib do not cure the treated cancers, clinical results suggest they are capable of partially stabilizing radioactive iodine–refractory thyroid cancer, according to three experts commenting on this intervention. Basing their analysis on the improvement in progression-free survival, they considered sorafenib and lenvatinib to have moderate potential to improve outcomes in patients. A head-to-head comparison of sorafenib to lenvatinib has not been performed, two clinicians noted. Such studies could help determine which agent would be most beneficial to patients. Another expert also noted the increased incidence of adverse events, which during the trial caused patients to lower their doses or prematurely discontinue treatment. The magnitude of the impact was lessened by the relatively small patient population that would be a candidate for the treatments and their oral route of administration, which limited any potential impact on health care staffing or infrastructure.
- **High-Impact Potential:** Lower end of the high-impact-potential range

# **Adolescent and Young Adult Oncology Intervention**

# Specialized Care Model for Adolescents and Young Adults With Cancer

**Unmet need:** Despite significant improvements in survival rates for pediatric and adult cancer patients during the past several decades, outcomes for adolescent and young adults (AYAs; age range, 13–30 years) with cancer have not improved, and some believe that care settings and models may be contributing factors.<sup>1-3</sup> AYAs who are hospitalized with cancer are often placed in pediatric units with much younger children or in adult cancer centers among much older patients. Both inpatient and outpatient standard care settings often fail to adapt to the life circumstances of AYAs, including demands of ongoing education, developing careers, and relationships and emotional and financial vulnerability.<sup>4</sup> The relative dearth of AYA oncologic clinicians and clinical trials targeted to this age group presents further challenges for determining the most effective care and delivering that care for these patients.<sup>5-7</sup>

**Intervention:** In late 2013, the Institute of Medicine partnered with the Livestrong Foundation to host a workshop for health care providers, researchers, and health advocates to raise awareness and discuss solutions for the unique issues surrounding AYA oncology and patient care, and published proceedings in January 2014.<sup>8</sup> One innovation with potential to address shortcomings in AYA cancer care is oncology programs dedicated solely to this patient population and staff that offer comprehensive, specialized, clinical and supportive care services for AYAs. Several dozen institutions have established AYA-directed oncology programs or support systems.<sup>8-10</sup> Although approaches to AYA-focused oncology programs vary, we describe one model, Teen Cancer America, brought to the United States that emerged from the UK Teenage Cancer Trust. This model illustrates the interventions that a comprehensive AYA-focused oncology program may entail,<sup>9,10</sup> although other models and funders of these models have emerged in the United States.

AYA specialized units typically offer inpatient and outpatient therapies on a modified schedule (i.e., chemotherapy sessions or medical procedures in the afternoon or evenings) to prevent excess disruption to the daily schedule of their AYA patients and promote treatment adherence.<sup>11</sup> Clinical spaces are designed to mimic the home environment, and dedicated spaces for education, peer social activities, family, and psychosocial therapy are often provided. For example, specially trained staff on Teen Cancer America/Teenage Cancer Trust AYA units include doctors and nurses specializing in common AYA cancers and care issues. They also develop extensive knowledge of clinical trial opportunities for AYAs, to develop evidence for AYA cancer care. Additionally, the units offer youth support coordinators who are trained to address the psychosocial and supportive care needs of AYA patients that arise during treatment and help to ease patients' transition back into school or work.<sup>12</sup> Because AYAs are more likely than younger children or older adults to be uninsured or underinsured, financial counseling is a critical aspect of the services offered to patients and their families, as is counseling regarding future fertility.<sup>13</sup>

The resources required to establish an AYA oncology unit vary, but typically begin with dedicated physical space distinct from pediatric or adult oncology wings. Resources are required to renovate or build units to create a home-like environment with clinical functionality. Structural modifications may include creating social, kitchen and dining, education, and recreation zones and tailored construction to conceal medical equipment.<sup>11</sup> Individual rooms and common areas are outfitted with personal computers, gaming systems, televisions, and so on.<sup>11</sup> Hospitals may need to recruit or train staff to provide AYA-specific clinical and supportive care. Care-team staffing requirements include clinical nurse specialists, youth support coordinators, and oncologists with experience in AYA malignancies and treatment.<sup>14</sup> Efforts to bolster clinical-trial enrollment and participation may require additional clinical staff and research resources.

**Clinical trials:** With the recent establishment and rapid growth of AYA programs, researchers, clinicians, and patients have begun to work collaboratively to establish metrics by which to collect data and assess health outcomes of patients treated in such programs or on AYA-dedicated oncology units.<sup>5,15</sup> Preliminary data demonstrated improved clinical trial enrollment among patients treated in an AYA oncology program.<sup>6</sup> An ongoing, large-scale study, BRIGHTLIGHT, was initiated in 2012 to gather qualitative and quantitative data from AYA oncology patients who received treatment on standard pediatric or adult units or AYA-specialized units.<sup>16</sup> As of November 2014, the study had enrolled 976 AYA patients with recent cancer diagnoses.<sup>17</sup> Data from this study should enable the first multicenter investigation of the impacts of AYA oncology units on patients, clinical-trial programs, and the health care system.

**Program developers and funding:** For the illustrative model we described, Teen Cancer America (Bala Cynwyd, PA)<sup>10</sup> is a nonprofit organization established in 2011 as the U.S. extension of Teenage Cancer Trust, a UK charity organization based in London.<sup>9</sup> These organizations formed partnerships with some hospitals and cancer centers to design and implement AYA cancer units.<sup>18</sup> Unit establishment requires collaborative efforts and support of the hospital, Teen Cancer America/Teenage Cancer Trust, and health care providers. As charitable organizations, Teen Cancer America and Teenage Cancer Trust coordinate and assume the fundraising and financial responsibilities for constructing and operating AYA units. Hospitals or cancer centers may also share financial costs, which run an estimated \$3 million to \$5 million to establish and outfit each AYA unit.<sup>9,10</sup> Other funders of AYA programs include the Lance Armstrong Foundation.

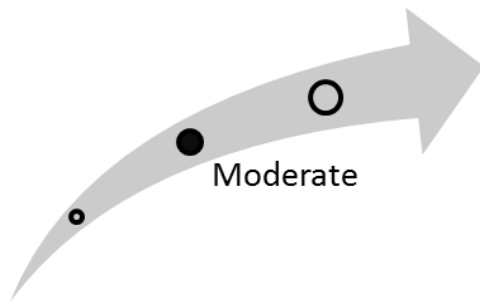
**Diffusion and cost:** Few data are available yet on the number of U.S. AYA cancer care programs, but searches have identified several dozen, some of which are part of the Teen Cancer America initiative. Since 1990, the Teenage Cancer Trust has funded 28 dedicated AYA oncology units throughout the United Kingdom<sup>19</sup> and the U.S. arm of the organization, Teen Cancer America, was launched in December 2011 and has established several programs here.<sup>20</sup> Teen Cancer America established the University of California, Los Angeles (UCLA) Medical Center Daltrey/Townshend Teen & Young Adult Cancer Program (Santa Monica, CA) in 2011 and opened its first AYA-dedicated oncology unit in the United States in November 2012.<sup>21</sup> As of September 2014, Teen Cancer America was reportedly in discussions with 30 facilities in 20 states regarding the development of AYA oncology programs.<sup>22</sup>

Numerous other cancer centers throughout the United States have established AYA oncology programs that provide dedicated services, programming, and/or space for AYA patients. For example, Seattle Children's Hospital announced in 2013 the establishment of the first inpatient unit dedicated to AYA cancer patients.<sup>23</sup> The number of medical centers advertising AYA-focused oncology programs has increased in recent years; some of these programs are sponsored by children's hospitals as a separate care unit; others are part of comprehensive cancer centers, such as the M.D. Anderson Cancer Center.<sup>5,24-32</sup>

## Current Approach to Care

Upon diagnosis of cancer, AYA patients often receive treatment at established pediatric or adult cancer centers. Care providers typically have a specialty in pediatric or adult oncology. Care settings and supportive services may be tailored to the predominant age range of a facility's patients. Recently, some cancer centers have begun to offer tailored supportive care services (i.e., psychosocial, educational, career support) to AYA patients, and facilities are incorporating dedicated social space for AYAs on many pediatric units. Other centers are offering supportive services geared to AYAs with cancer to address some of the needs of this patient population.<sup>8</sup>

**Figure 1. Overall high-impact potential: specialized care model for adolescents and young adults with cancer**



Most experts commenting on this program agreed that an unmet exists for health care models focusing on AYAs. However, two were concerned that few clinical data are available yet demonstrating improved health outcomes in AYAs treated under such programs. One clinician in particular was concerned that this care model would require costly structural and administrative changes, which might be carried out before evidence is available to demonstrate improved AYA health outcomes from such programs. If these programs are widely implemented, experts thought, clinicians and patients would be very accepting of the models. However, the experts' opinions differed on the effects this intervention would have on health disparities: some experts thought it would increase disparities because AYA centers would not be available to all AYA cancer patients; others, with clinical perspectives, thought it would decrease health disparities between AYAs and non-AYAs. Based on this input, our overall assessment is that this intervention has moderate high-impact-potential.

## **Results and Discussion of Comments**

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.<sup>33-38</sup> We have organized the following discussion of expert comments by the parameters on which they commented.

**Unmet need and health outcomes:** Experts are aware of the physical and emotional needs AYAs have during cancer care, which are not always addressed by standard pediatric and adult cancer health care systems. Although an unmet need exists for specialized AYA care models, noted the experts, data on health improvement are necessary to determine the actual benefits such programs will confer. In contrast, one expert thought that AYA health outcomes are influenced more by the lack of health insurance than by not having access to AYA specialized care. The program has moderate potential to improve AYA patient outcomes, experts thought.

**Acceptance and adoption:** Experts anticipate most clinicians are likely to adopt this specialized program for AYAs, and that expectation appears on the way to being fulfilled as dozens of AYA cancer programs have emerged since experts submitted their comments. One expert thought acceptance would be slow at first, but acceptance would accelerate as more health centers adopt AYA health care programs.<sup>37</sup> Another expert thought additional training requirements and insufficient evidence of improved health outcomes at this time would hinder clinical acceptance.<sup>35</sup> Experts agreed unanimously that AYA patients and their families would be very accepting of this care model.

**Health care delivery infrastructure and patient management:** Most experts thought specialized AYA oncology units would have moderate impact on health care delivery infrastructure and patient management. They indicated that oncology wings could be adapted for AYA treatment with modest renovations, although one health systems expert and one research expert anticipated that hospitals would dedicate new physical space and infrastructure for this purpose.<sup>33,38</sup> Overall,

experts anticipated minimal change to the prescribed AYA patient treatment regimens, but noted patients would benefit from having access to counselors and other clinical care resources focusing on AYA health outcomes and wellbeing.

**Health disparities:** Experts had differing opinions on the impact specialized AYA care models would have on health disparities. Three experts thought that if diffusion of AYA health centers was slow, it could increase health disparities due to limited accessibility by patients in some geographic areas. However, both a clinical and a research expert commenting on this program suggested it has potential to minimize health disparities between AYAs and non-AYAs, including for patients who lack family support.<sup>36,38</sup>

## **Breast Cancer Interventions**

## Ado-Trastuzumab Emtansine (Kadcyla) Antibody-Drug Conjugate for Treatment of Advanced HER2-Positive Breast Cancer

**Unmet need:** Human epidermal growth factor 2 (HER2)-positive breast cancer is a subclass of invasive breast cancer characterized by the expression of high levels of the epidermal growth factor receptor (EGFR) family member, HER2, and it comprises about 20% of breast cancer cases. Historically, HER2-positive breast cancer has been associated with more aggressive disease and poor outcomes; however, the dependence of HER2-positive breast cancers on HER2 activity has also provided a clearly defined molecular target.<sup>39</sup> Outcomes for patients with HER2-positive breast cancer have improved with the availability of targeted therapies such as the HER2-specific monoclonal antibody trastuzumab and the HER2 kinase inhibitor lapatinib; however, even with these treatments, many patients with metastatic HER2-positive breast cancer still experience disease progression. Therefore, compounds with improved efficacy are highly desired.<sup>40</sup> Standard therapies for HER2-positive metastatic disease typically employ a HER2-targeted agent in combination with a systemically administered cytotoxic drug. One approach to improve HER2-positive breast cancer treatment is the development of antibody drug complexes (ADCs) that conjugate a highly cytotoxic agent to a HER2-specific antibody. These compounds purportedly deliver a cytotoxic drug to HER2-overexpressing cells, potentially improving efficacy while limiting exposure of nontumor tissues to the cytotoxic agent. Additionally, these agents could be administered as monotherapies, obviating the need for nontargeted cytotoxic therapy, potentially improving the treatment's adverse-event profile. The first ADC approved by the U.S. Food and Drug Administration (FDA) for treating breast cancer was ado-trastuzumab emtansine (Kadcyla<sup>®</sup>), which was approved in February 2013 for treating patients who have HER2-positive metastatic breast cancer and have previously received trastuzumab and a taxane.<sup>41</sup>

**Intervention:** Ado-trastuzumab emtansine is an ADC of trastuzumab, a HER2-targeted monoclonal antibody, and DM1, a highly cytotoxic agent.<sup>42</sup> The ADC is designed to allow targeted delivery of the cytotoxic agent to HER2-expressing tumor cells.

Trastuzumab is a recombinant humanized antibody that binds the extracellular domain of HER2 receptors present at the cell surface. Antibody binding to HER2 leads to receptor internalization via endocytosis. Trastuzumab reduces activity of the PI3K signaling cascade, causes cell cycle arrest, inhibits angiogenesis, and stimulates antibody-dependent cell-mediated cytotoxicity.<sup>43</sup>

DM1 is a derivative of maytansine and is a microtubule assembly inhibitor with potent cytotoxic effects.<sup>42</sup> Maytansinoids (e.g., DM1) are too toxic to be administered alone but have been linked to various antibodies to create investigational, targeted therapies.<sup>44</sup>

To create ado-trastuzumab emtansine, trastuzumab is covalently linked to DM1 by a stable chemical linker (i.e., the thioether linker MCC [4-(N-maleimidomethyl) cyclohexane-1-carboxylate]). The DM1-MCC complex is referred to as emtansine. Ado-trastuzumab emtansine contains about 3.5 DM1 molecules per trastuzumab antibody.<sup>42</sup>

Ado-trastuzumab emtansine's ADC formulation holds DM1 in a stable, inactive form outside the cell. Upon cellular uptake of the ADC, which is mediated by the antibody's binding to the HER2 receptor, DM1 enters the cell and lysosomal degradation releases its molecules into the intracellular space.<sup>42,44</sup> In this way, DM1 is preferentially targeted to tumor cells that express high levels of HER2, purportedly sparing many normal tissues from the drug's toxic effects. By supplying a cytotoxic drug in this linked manner, treatment with ado-trastuzumab emtansine may obviate the need for co-administration of systemic cytotoxic chemotherapy, which is a cause of



significant toxicity in HER-2 targeted regimens such as trastuzumab plus taxane and lapatinib plus capecitabine.

Preclinical studies demonstrated that ado-trastuzumab emtansine retains the antiproliferative activity of trastuzumab and is able to inhibit the growth of lapatinib- and trastuzumab-resistant HER2-positive breast cancer cells.<sup>43,45</sup> The cytotoxic activity of DM1 may endow the compound with additional antitumor properties even in tumors that are independent of HER2 signaling (a hallmark of some tumors that have become resistant to trastuzumab and/or lapatinib).

Ado-trastuzumab emtansine is an intravenous (IV) medication that is administered at dosage of 3.6 mg/kg, once every 3 weeks. In treating locally advanced/metastatic disease, the drug is administered until disease progression or unacceptable toxicity occurs in the patient.<sup>42</sup>

**Clinical trials:** Ado-trastuzumab emtansine is being studied in a number of trials in patients with metastatic disease. In 2012, investigators published results from the phase III EMILIA trial, which compared treatment with ado-trastuzumab emtansine to standard therapy (lapatinib plus capecitabine) in patients with metastatic, HER2-positive breast cancer previously exposed to trastuzumab. In this randomized, open-label trial, investigators reported improved progression-free and overall survival in patients receiving ado-trastuzumab emtansine compared with patients receiving lapatinib plus capecitabine (median progression-free survival 9.6 months and 6.4 months, respectively; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.55 to 0.77;  $p < 0.001$ ; overall survival at second interim analysis was 30.9 months and 25.1 months, respectively; HR, 0.68; 95% CI, 0.55 to 0.85;  $p < 0.001$ ). Fewer patients in the ado-trastuzumab emtansine arm than in the lapatinib plus capecitabine arm experienced grade 3 or 4 adverse events (41% and 57%, respectively).<sup>46</sup>

In 2014, investigators published results from the phase III TH3RESA trial, which compared ado-trastuzumab emtansine to treatment of physician's choice in treating patients with metastatic disease who had undergone multiple therapies including trastuzumab and lapatinib.<sup>47</sup> In this randomized, open-label trial, investigators reported that patients who received ado-trastuzumab emtansine exhibited increased progression-free survival (6.2 vs. 3.3 months, stratified HR, 0.528; 95% CI, 0.422 to 0.661;  $p < 0.0001$ ) while simultaneously reducing the overall incidence of grade 3 or higher adverse events.<sup>47</sup>

A third phase III trial (MARIANNE) in metastatic disease is studying a combination of trastuzumab and pertuzumab in the first-line setting.<sup>48</sup> Besides these studies in patients with metastatic disease, ado-trastuzumab emtansine is also under study for treating nonmetastatic breast cancer as a neoadjuvant (presurgery) and as an adjuvant (postsurgery) treatment option.<sup>49-51</sup>

**Manufacturer and regulatory status:** Ado-trastuzumab emtansine is manufactured by the Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland. The EMILIA study provided the basis for Roche's ado-trastuzumab emtansine biologic license application to FDA, which granted it priority review status in November 2012.<sup>52</sup> In February 2013, FDA approved ado-trastuzumab emtansine for treating "patients with HER2-positive (HER2+), metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination."<sup>41,53</sup> The prescribing information notes that patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.<sup>53</sup>

**Diffusion and cost:** Roche announced pricing of ado-trastuzumab emtansine at \$9,800 per month of treatment.<sup>54</sup> However, discount coupons have been available. The biologic is given at a dosage of 3.6 mg/kg every 3 weeks (21-day cycle) until disease progresses or unacceptable toxicity develops in the patient. Thus, a 70 kg (154 lb) person would require about 252 mg. The drug is provided in 100 mg vials. A U.S.-based, online aggregator of prescription-drug prices, GoodRx, listed costs as of August 2014 of about \$2,800 to \$3,000 for a single 100 mg vial.<sup>55</sup> This pricing

required use of a discount coupon. If one 70 kg patient required about 2.5 vials, the cost would be about \$7,500 per infusion cycle if the hospital pharmacy preparing the infusion is able to use the remainder in the vial for another patient. If not, then the cost would be about \$9,000 per infusion cycle for a patient of this weight. In the EMILIA clinical trial, patients in the ado-trastuzumab emtansine arm received treatment for a median of 7.6 months (approximately 8 cycles);<sup>42</sup> therefore, the cost of an ado-trastuzumab treatment regimen in the approved indication would be approximately \$72,000.

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) found 7 payers with policies regarding ado-trastuzumab emtansine.<sup>56-62</sup> All payers with identified policies consider this agent to be medically necessary when prescribed according to FDA-approved indications (HER2-positive, metastatic breast cancer in patients who previously received trastuzumab). As an IV medication administered in the health care setting, ado-trastuzumab emtansine may be covered under Medicare Part B benefits.

The U.S. Centers for Medicare & Medicaid Services (CMS) has assigned a Healthcare Common Procedure Coding System (HCPCS) Level II code (i.e., C9131) to describe the injection of 1 mg of ado-trastuzumab emtansine; this code may be reported multiple times to describe the administered dose of the drug.<sup>63</sup>

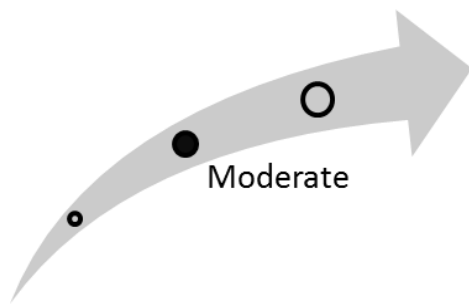
## **Clinical Pathway at Point of This Intervention**

Typical adjuvant and neoadjuvant treatment regimens include chemotherapy (e.g., doxorubicin/cyclophosphamide, fluorouracil/epirubicin/cyclophosphamide) followed by a taxane (e.g., docetaxel, paclitaxel) plus trastuzumab.<sup>64</sup> Pertuzumab may also be used as an adjunct to taxane and trastuzumab. In this setting, ado-trastuzumab emtansine is being studied in the KAITLIN trial in combination with pertuzumab (i.e., ado-trastuzumab emtansine replacing taxane plus trastuzumab).<sup>49</sup> Additionally, ado-trastuzumab emtansine is being studied in the KATHERINE trial in patients who had residual disease after completing neoadjuvant therapy.<sup>51</sup>

Patients with HER2-positive breast cancer that is locally advanced or has become metastatic and is untreatable by surgical resection are typically treated using a series of HER2-targeted therapies. Standard first-line therapy typically includes treatment with trastuzumab plus a single cytotoxic chemotherapy agent (e.g., capecitabine, docetaxel, paclitaxel, vinorelbine). More recently, a three-drug regimen of trastuzumab, pertuzumab, and docetaxel has been used in the first-line setting. For treating locally advanced/metastatic disease, ado-trastuzumab emtansine is being studied in the MARIANNE trial as either a monotherapy or in combination with pertuzumab.<sup>65</sup> Therefore, in this setting, ado-trastuzumab emtansine could compete with standard trastuzumab plus taxane and could compete with or complement use of pertuzumab.

Patients whose disease progresses after first-line therapy are typically treated with a second HER2-targeted therapy, typically lapatinib plus capecitabine. Alternative second-line chemotherapy options include trastuzumab plus a cytotoxic agent that was not used in first-line treatment or trastuzumab plus lapatinib.<sup>66</sup> The recent FDA approval of ado-trastuzumab emtansine in the second-line setting provides new treatment options for patients with metastatic breast cancer.

**Figure 2. Overall high-impact potential: ado-trastuzumab emtansine (Kadcyla) antibody-drug conjugate for advanced HER2-positive breast cancer**



Ado-trastuzumab emtansine has significant potential to improve outcomes for patients with HER2-positive metastatic breast cancer, opined experts who commented on this intervention. They thought the shortcomings of previous therapies represented a significant unmet need. Additionally, they thought ado-trastuzumab emtansine's potential to displace current standard of care for HER2-positive metastatic breast cancer could have significant impacts on patient management. If results from additional studies continue to be favorable, experts believe, ado-trastuzumab emtansine could be used on a wider patient population as first-line treatment as well as second-line treatment for advanced HER2-positive breast cancer. They also thought its cost was comparable to monthly costs of other targeted cancer therapies. 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 ado-trastuzumab emtansine for treating breast cancer.<sup>67-72</sup> We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** Experts commenting on ado-trastuzumab emtansine agreed it has potential to address an unmet need. Patients with HER2-positive breast cancer have poor outcomes because they have no effective second-line options if their disease progresses after first-line treatment, two clinicians remarked. They thought ado-trastuzumab emtansine has the potential to improve outcomes in this patient population.<sup>67,71</sup> Experts pointed out results from the EMILIA trial demonstrated a significant extension in progression-free and overall survival and a decrease in adverse events for patients treated with ado-trastuzumab emtansine versus those outcomes in patients treated with lapatinib plus capecitabine. Additionally, an expert clinician also thought ado-trastuzumab emtansine could possibly be more efficacious if patients received treatment in combination with other HER2-positive interventions (i.e. pertuzumab).<sup>71</sup>

**Acceptance and adoption:** Ado-trastuzumab emtansine will be readily adopted by physicians and patients, experts agreed unanimously. Reasons for considering adoption included its potential to improve overall patient outcomes, manageable adverse events, route of administration, and its option as a treatment for patients with recurrent breast cancer. However, the high cost of ado-trastuzumab emtansine was one potential barrier raised by an expert.<sup>69</sup>

**Health care delivery infrastructure and patient management:** Ado-trastuzumab emtansine is not expected to disrupt treatment delivery or the way patients are managed, experts thought. Cancer centers that already administer IV infusions would need no infrastructure or staffing change to offer ado-trastuzumab emtansine, experts agreed. However, a clinician pointed out that oncologists would need to learn about the drug and how to administer it and would need to monitor patients in case they manifest serious adverse events; however, this is routine procedure for any IV infused drug for cancer patients.<sup>67</sup>

**Health disparities:** Ado-trastuzumab emtansine has a small potential to affect health disparities, the experts indicated. However, one expert raised a concern that the anticipated high price of the drug could increase health disparities in patients with low socioeconomic status who have no health insurance.<sup>72</sup> Similarly, one clinician expected that breast cancer disparities may worsen if ado-trastuzumab emtansine is adopted primarily by women with higher socioeconomic status.<sup>67</sup> Contrarily, the other experts noted the drug would be added to current regimens; therefore, most costs would be absorbed directly by third-party payers (or indirectly by patients if insurance premiums and co-pays increase).

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

**Unmet need:** The American Cancer Society (ACS) estimates that in 2014, more than 230,000 cases of invasive breast cancer will be diagnosed in the United States.<sup>73</sup> In 75% of diagnosed breast cancers, tumor cells express high levels of the estrogen receptor, which is called estrogen receptor–positive (ER+) disease. Patients with ER+ breast cancer have many therapeutic alternatives available to them. They 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+ breast cancer die of the disease.<sup>74</sup> 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.<sup>75,76</sup> Similar to other types of cancer, ER+ breast cancer cells frequently have overactivated CDK 4 and 6 and overexpressed cyclin D. Palbociclib purportedly targets and selectively inhibits CDKs 4 and 6 to block cell-cycle progression and inhibit proliferation of tumor cells.<sup>75,77</sup> Several phase III trials are testing palbociclib in multiple ER+ breast cancer treatment settings.<sup>78</sup>

**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.<sup>74,75</sup> To prevent uncontrolled cell growth, 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.<sup>74,75</sup> 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.<sup>75,79</sup> 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, no CDK inhibitor has been approved by 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.<sup>79</sup>

ER+ breast cancer cells may be particularly sensitive to CDK 4/6 inhibition.<sup>75</sup> In luminal breast cells, progesterone and estrogen drive cell proliferation by binding to progesterone receptor (PR) and ER respectively. In ER+ 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+ 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 ER+ breast cancer treatment with manageable side effects; however, up to 50% of patients with ER+ breast cancer will develop endocrine-therapy resistance.<sup>80-82</sup> 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.<sup>75</sup> Additionally, gene-expression profiles have identified CDK6 overexpression to be associated with fulvestrant resistance in breast cancer cells.<sup>80</sup> 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 dose of 125 mg, daily, in 28-day cycles with 21 days on treatment followed by 7 days off.<sup>83-86</sup>

**Clinical trials:** Palbociclib is being tested primarily as first-line treatment of locoregionally recurrent or metastatic ER+ breast cancer in combination with letrozole in postmenopausal women.<sup>83,87</sup> 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.<sup>88</sup> Patients treated with palbociclib (125 mg daily, for 3 out of 4 weeks) and letrozole (continuous 2.5 mg daily) or were treated with 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; HR, 0.49;  $p < 0.0004$ ). Additionally, 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;  $p < 0.2105$ ).<sup>88</sup>

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:<sup>88</sup>

- 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 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).<sup>85,86</sup> Additionally, 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).<sup>84</sup>

**Manufacturer and regulatory status:** Pfizer, Inc., New York, NY, is developing palbociclib. In April 2013, basing its decision on results from the phase II PALOMA-1 trial, FDA granted palbociclib breakthrough therapy status for treating women with advanced ER+/HER2- (human EGFR 2–negative) breast cancer.<sup>76</sup> Data from PALOMA-1 also served as the basis for a new drug application (NDA) submitted to FDA, and in October 2014, FDA granted priority review for the application. The FDA meeting is scheduled for April 2015.<sup>89,90</sup>

**Diffusion and cost:** No specific cost information is available at this time. If FDA approves palbociclib and clinical data prove that it is a viable, safe breast cancer therapy, third-party payers

will likely include palbociclib on their formularies as a specialty pharmaceutical requiring prior authorization for coverage.

## Clinical Pathway at Point of This Intervention

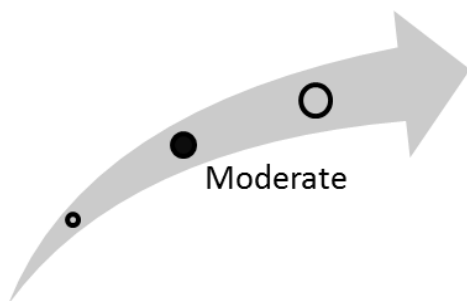
The majority of palbociclib studies are assessing the drug's activity in patients undergoing systemic treatment for locally advanced or metastatic breast cancer. Patients with locally advanced or metastatic ER+ breast cancer are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens 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 multiple endocrine therapies.<sup>91</sup> 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

Additionally, 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.<sup>91</sup> 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., LEE011, abemaciclib) are also under study for treating breast cancer and could eventually compete with palbociclib.<sup>79</sup>

**Figure 3. Overall high-impact potential: palbociclib (Ibrance) for treatment of advanced estrogen receptor-positive breast cancer**



Most experts including two clinicians, understand 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, two health technology assessment experts thought the potential to address the unmet need was small, basing their assessment on the lack of efficacy data thus far. 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, and health systems backgrounds, offered perspectives on the topic of palbociclib for treating ER+ breast cancer.<sup>92-97</sup> 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 estrogen receptor 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.<sup>97</sup> 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, 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 did not think results from the ongoing phase II trial successfully demonstrate that benefits outweigh the increased incidence of adverse events.<sup>95,97</sup> 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.<sup>93,96</sup>

**Health care delivery infrastructure and patient management:** Experts anticipated that as an orally administered medication, palbociclib use would not significantly shift health care staffing or infrastructure. Additionally, 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 impact health care costs, experts anticipated. Although palbociclib is not FDA approved and has no specific cost information, experts assume it will be priced similar to other cancer drugs. However, with demonstrated efficacy it could receive regulatory approval and would likely be covered as a specialty drug requiring prior authorization. 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 than IV drugs.<sup>92,93</sup> A caveat is that if palbociclib is labeled as second-line treatment, many low-income patients may not receive IV infusion with first-line treatments and may be limited in their access to palbociclib.



## **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.<sup>98</sup> 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.<sup>99</sup> 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

Integration of the methylation marker, mutation marker, and hemoglobin results generates a positive or negative result based on cutoffs established by prior analysis of known samples.<sup>100</sup>

The Exact Sciences CRC screening test is designed to be integrated easily into routine laboratory schedules and automated systems.<sup>99,101</sup>

**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 multitarget stool DNA test to detect colorectal cancer, 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 multitarget 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 multitarget stool DNA testing and FIT were 86.6% and 94.9%, respectively. In a patient population at average risk for CRC, the number of individuals who would needed to be screened to detect one cancer was reported as 154 for colonoscopy, 166 for multitarget stool DNA testing, and 208 for FIT.<sup>102</sup>

**Manufacturer and regulatory status:** Exact Sciences Corp. (Madison, WI) developed the Cologuard stool DNA screening test. In August 2014, FDA approved marketing of the Cologuard test as a colorectal cancer screening option.<sup>103</sup> 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.”<sup>104</sup>

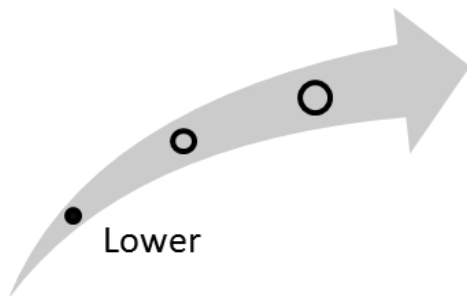
**Diffusion and cost:** In October 2014, CMS used its new parallel review process (which enables CMS coverage review at the same time as FDA regulatory approval review to enable a coverage decision to be in place around the time a technology is FDA approved) for the first time to issue a national coverage determination (NCD) for Cologuard. 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 colorectal cancer; and are at average risk of developing colorectal cancer.<sup>105</sup> The NCD is expected to aid rapid adoption of the test.

Cologuard’s retail price has been reported as \$600 per test.<sup>106</sup> 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.<sup>107</sup>

## 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.<sup>108</sup> For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps.<sup>108</sup> 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 4. Overall high-impact potential: multitarget stool DNA molecular test (Cologuard) for colorectal cancer screening**



Overall, experts suggested that multitarget stool DNA testing has potential to improve on the accuracy of current noninvasive stool-based tests such as FOBT or FIT, which could improve screening results. However, the biggest shifts in patient outcomes and management were envisioned in patients who would switch from colonoscopy to stool DNA testing or patients currently unscreened now opting for stool DNA testing, and experts commenting questioned whether these changes in screening patterns were likely; therefore, our overall assessment is that Cologuard is at the lower end of the high-impact-potential range. However these comments were received in May 2014, before FDA approval and CMS coverage; thus, we will seek additional comments to determine if expert views have changed.

## Results and Discussion of Comments

Six experts, with clinical, research, health devices, and health systems backgrounds, offered perspectives on this topic.<sup>109-114</sup> These comments were received in May 2014, before FDA approval and CMS coverage. We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** Experts commenting considered the unmet need for improving on existing CRC cancer screening methods to be moderately or very important. They cited the large number of individuals who are not adherent with CRC screening recommendations despite the clear benefits of CRC screening on survival; experts suggested that additional testing options could lead to additional patients being screened.

The multitarget stool DNA test's potential to improve patient health is moderate according to the majority of experts commenting. On one hand, commenters cited the potential of a new noninvasive test to improve screening adherence and suggested that it represents an improvement over existing fecal tests testing only for presence of blood (i.e., FIT, FOBT) alone. However, commenters also noted that although the test demonstrated an improved sensitivity for CRC and precancerous lesions, no trial had indicated that this increase in sensitivity led to improved patient health outcomes. Additionally, commenters questioned whether results from a trial involving a one-time test could be extrapolated to the standard screening setting in which FIT or FOBT is performed annually. Lastly, although several commenters suggested that the multitarget stool DNA test could increase screening adherence, one expert with a health systems perspective noted that, like FIT and FOBT, Cologuard is still a fecal-based test requiring the patient to collect and return a stool sample, which some patients may find objectionable.<sup>110</sup>

**Acceptance and adoption:** Expert comments on acceptance and adoption varied depending on whether the commenter viewed the multitarget stool DNA test as an alternative to FIT/FOBT or as an alternative to colonoscopy. Experts who saw the stool DNA test as competing with FIT/FOBT did not foresee large barriers to adoption and suggested that multitarget stool DNA testing could supplant these other noninvasive tests. Experts who saw the multitarget stool DNA test as competing with colonoscopy suggested that clinicians would be unlikely to recommend the stool DNA test over colonoscopy and, therefore, the stool DNA test would likely be reserved for the portion of the screening population that refuses colonoscopy. One commenter with a research perspective suggested that clinicians' high degree of familiarity with existing test methods could pose a barrier to adoption of a new test and that further study might be needed to identify the best position for the multitarget stool DNA test within the CRC screening test menu.<sup>113</sup> A commenter with a clinical perspective suggested that some patients who are highly motivated to undergo screening might opt for both colonoscopy and stool DNA testing.<sup>112</sup>

**Health care delivery infrastructure and patient management:** Expert comments on potential changes to health care delivery infrastructure and patient management again diverged according to whether the commenter viewed the multitarget stool DNA 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 moderate shifts in both infrastructure and patient management. They cited the reduction in demand for screening colonoscopy and a shift of required resources from endoscopy suites to the clinical laboratory. Whereas if the multitarget stool DNA test were to replace other noninvasive tests, the majority of commenters thought, little change would be seen in health care infrastructure or patient management outside a potential change in the frequency of testing. One expert with a health devices perspective suggested that the adoption of multitarget stool DNA testing among non-screening-compliant patients could lead to an increase in demand for colonoscopy services.<sup>111</sup>

**Health Disparities:** Experts commenting did not envision that the availability of multitarget stool DNA testing would have a significant impact on health disparities. Although some commenters suggested that an improved noninvasive test option could improve screening among underserved patient populations that might not have easy access to colonoscopy, other commenters suggested that the likely increased cost of multitarget stool DNA testing relative to FIT/FOBT could further exacerbate existing health disparities if this cost difference restricts its use.

## **Fertility Issues Associated with Gonadotoxic Cancer Therapy**

## Ovarian Tissue Cryopreservation for Fertility Preservation in Women 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 gonadotoxic and can permanently impair fertility.<sup>115,116</sup> Prepubertal girls, 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 with patients with clinicians and counselors. In vitro fertilization with subsequent embryo cryopreservation is the only standard option available to girls and women who wish to be able to have children after cancer remission.<sup>117</sup> However, this procedure is not available to prepubertal females. Additionally, this option requires weeks of ovarian stimulation with hormones to mature the follicles/oocytes and, therefore, the ovarian stimulation process may be contraindicated for women who must urgently begin treatment or whose cancers may worsen with hormone treatments.<sup>118</sup> 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.<sup>119</sup>

**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.<sup>117</sup> Tissue harvesting can coincide with oophorectomy, and an ovarian biopsy specimen may be sent for histopathological analysis to rule out the presence of malignant cells.<sup>120</sup> Typically, the cortex from at least one ovary is sectioned (about 1.0–1.5 mm thick, to ensure inclusion of 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 off-site laboratories of tissue banks.<sup>121</sup>

Once a patient completes treatment, reimplantation of the cryopreserved ovarian tissue is performed 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).<sup>117,121</sup> 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.<sup>121</sup>

As an alternative, surgeons can also place the autograph in a heterotopic location such as the abdominal wall, forearm, or rectus muscle,<sup>117,120,121</sup> 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.<sup>120-122</sup>

**Clinical trials:** Multiple nonrandomized trials are ongoing to examine ovarian tissue cryopreservation in adult females who require gonadotoxic therapies to treat a variety of malignant conditions.<sup>123-128</sup> 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.

A 2014 review indicates that 30 live births have been reported worldwide in women who underwent transplantation of autologous cryopreserved ovarian tissue.<sup>129</sup> The majority of these cases have been reported in small series or single case reports.<sup>130-135</sup> 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.<sup>136</sup> Fertility outcomes were available for 114 of these patients of whom 40 (~35%) experienced premature ovarian failure. Eight of these 40 patients underwent ovarian tissue transplantation, which resulted in three pregnancies. Additionally, Dolmans and colleagues reported a 15-year retrospective analysis of 476 patients who underwent ovarian tissue cryopreservation for fertility preservation.<sup>137</sup> Among these patients, 11 patients underwent autotransplantation, resulting in 5 live births and 1 ongoing pregnancy.

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.<sup>138</sup> Recent retrospective studies have detected cancerous cells in only a small minority of ovarian tissue samples taken from patients;<sup>136,137</sup> 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 are being pursued.<sup>138</sup>

**Manufacturer and regulatory status:** A number of medical institutions in the United States offer ovarian tissue cryopreservation as a service for female patients with cancer who wish to preserve their fertility.<sup>139</sup> Additionally, 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, Philadelphia<sup>126</sup>
- Boston IVF, Boston, MA<sup>127</sup>
- Hadassah Medical Center, Jerusalem, Israel<sup>123</sup>
- Oregon Health & Science University, Portland<sup>128</sup>
- University of Kansas Medical Center Research Institute, Kansas City<sup>124</sup>
- Weill Medical College of Cornell University, New York, NY<sup>125</sup>

Additionally, the Oncofertility Consortium<sup>®</sup> 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.<sup>140</sup>

**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).<sup>141-145</sup> 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.<sup>146</sup> Such coverage may occur more on a case-by-case basis than as under the umbrella of an overall medical coverage policy.

An economic evaluation of fertility preservation treatments determined the procedure for cryopreserving ovarian tissue would cost approximately \$27,000.<sup>147</sup> The estimated fees published online from a fertility clinic 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 preparation of 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 previous estimate once storage costs are included.<sup>148</sup> 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-\$38 per month for storage.<sup>149</sup> Other facilities charge yearly fees that range between \$350 and \$425.<sup>148,150</sup>

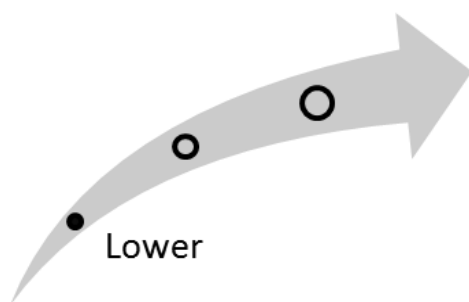
## Clinical Pathway at Point of This Intervention

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.<sup>151</sup>

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.<sup>116,117</sup> 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.<sup>117</sup>

Besides ovarian tissue cryopreservation, several investigational approaches exist for fertility preservation: oocyte cryopreservation, oocyte in vitro maturation, and pharmacological ovarian suppression.<sup>118</sup> With the exception of gonadal shielding and ovarian transposition to prevent radiation exposure, these fertility preservation options are limited to reproductive-age women.

**Figure 5. Overall high impact potential: ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer therapy**



Experts commenting on this topic were often divided in their assessment of this intervention, which reflects in part some controversies over fertility preservation for female oncology patients



and fertility as a therapy overall. Some experts stated that this intervention filled an extremely important unmet need for female cancer patients, while others indicated that fertility preservation was 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 with the potential to increase the likelihood of fertility preservation, 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.<sup>152-157</sup> We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** Experts were divided 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 regarding 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 represented a very important complement to existing methods.<sup>153</sup> Conversely, one expert with a clinical engineering perspective indicated that the magnitude of the unmet need potentially addressed by ovarian tissue cryopreservation was of little to no importance, suggesting that only a small number of prepubertal patients would be served by the addition of ovarian tissue cryopreservation to existing methods.<sup>157</sup> 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 women who experience premature ovarian failure due to gonadotoxic chemotherapy; however, multiple commenters questioned whether loss of child-bearing potential represented a significant unmet medical need relative to other health care needs.

Experts commenting 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.<sup>153</sup> Conversely, one expert with a clinical engineering perspective suggested that ovarian tissue cryopreservation has no potential to change or improve patient health outcomes.<sup>157</sup> Experts viewing the procedure's potential to improve patient health as minimal to moderate 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 in magnitude; 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 divided in their opinions regarding the likelihood of clinician acceptance and adoption. Commenters indicating 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 available to physicians. Commenters who thought adoption would be low by clinicians 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 reintroduction of cancer.

The majority of commenters thought that moderate to wide adoption of this intervention by patients was likely. These commenters cited the relatively low risks involved in the ovarian tissue collection procedure and patient desire for options to preserve fertility. However, multiple experts noted that the high cost of this procedure and the potential lack of reimbursement by insurers could limit 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.<sup>154,156</sup>

**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. Commenters 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 represented another option to cryopreserving embryos or oocytes. Multiple commenters envisioned small disruption to the care pathway because of the invasive nature of the procedure and the need to coordinate cancer treatment with a fertility preservation regimen. However, one expert with a clinical perspective 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, specifically.<sup>153</sup>

**Health disparities:** Because this procedure is likely to be associated with substantial cost and coverage may be unlikely, experts concurred that this option would likely be available only to economically advantaged patients. This may further increase health disparities for women and families 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.<sup>158</sup> Despite recent advancements in surgical techniques, radiotherapy, and chemotherapy, the prognosis for these patients remains poor.<sup>159</sup> 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.<sup>158,160,161</sup>

**Intervention:** Vascular endothelial growth factors (VEGFs) are highly expressed by many tumor types and are thought to signal to their cognate receptors (e.g., VEGF receptor 2 [VEGFR2]) on endothelial cells, promoting these cells' proliferation, migration, and survival. These processes are essential to angiogenesis, which is thought to be required for both the growth of large tumors and the 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 rational for this approach.<sup>158,162-164</sup>

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 multiple VEGFs exist, targeting a single VEGF may allow residual VEGFR activation by other ligands. Conversely, because available small-molecule kinase inhibitors simultaneously modulate multiple signaling pathways, they may have less favorable efficacy or toxicity profiles than agents of greater specificity.

Ramucirumab (Cyramza<sup>®</sup>) 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.<sup>165,166</sup> 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.<sup>166</sup> Among VEGFR2-specific agents, ramucirumab is furthest along in development.<sup>165</sup> Ramucirumab is administered intravenously at a dosage of 8 mg/kg every 2 weeks.<sup>167</sup>

**Clinical trials:** Ramucirumab has been tested as second-line monotherapy for gastric cancer (REGARD trial)<sup>168</sup> and as combination therapy with paclitaxel (RAINBOW trial).<sup>169,170</sup>

Results from a phase III, randomized, double-blind, placebo-controlled trial of 355 patients (REGARD) were published in 2014.<sup>168</sup> 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).<sup>168</sup>

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. Additionally, 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.<sup>168</sup> As monotherapy, ramucirumab treatment was tolerated by patients. The drug's prescribing information lists the most common side effects observed in patients with advanced gastric cancer: hypertension and diarrhea.<sup>167</sup> In the REGARD trial, the most common grade 3 adverse events experienced by patients were as follows:<sup>167,168</sup>

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

As a combination therapy, ramucirumab and paclitaxel treatment 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;  $p=0.0169$ ).<sup>169,170</sup>

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:<sup>169</sup>

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

**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, Eli Lilly submitted a biologics license application (BLA) to FDA for ramucirumab monotherapy for gastric cancer. FDA granted the BLA priority review and approved ramucirumab in April 2014 for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma, after fluoropyrimidine/platinum-based chemotherapy.<sup>171</sup> 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.<sup>172</sup> In December 2014, based on the results of the phase III REVEL trial, FDA approved ramucirumab in combination with docetaxel for treating patients with metastatic nonsmall cell lung cancer (NSCLC) whose disease has progressed after platinum-based chemotherapy. This indication is also intended as treatment for NSCLC caused by genetic alterations in either EGFR or anaplastic lymphoma kinase (ALK) and that has progressed after targeted therapy.<sup>173</sup>

**Diffusion and cost:** According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the retail price for six vials (a single dose for a patient weighing 70 kg) of Cyramza (100 mg/10 mL) ranged between \$5,900 and \$6,900 with use of a coupon.<sup>174</sup>

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 regarding ramucirumab.<sup>175-180</sup> These payers consider this agent to be medically necessary when prescribed according to FDA-approved indications. 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 multiple times to describe the administered dose of the drug.<sup>181</sup>

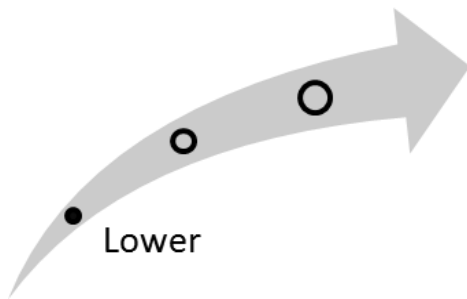
## Clinical Pathway at Point of This Intervention

Metastatic gastric cancer is typically treated with systemic chemotherapy.<sup>161,182</sup> 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 EGFR2–positive disease).<sup>159,161,164</sup> 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.<sup>163,164</sup>

In clinical trials for gastric cancer, ramucirumab is administered in combination with paclitaxel or best supportive care in second-line treatment. Ramucirumab is likely to be part of combination therapy for metastatic disease that includes other systemic chemotherapies or targeted therapies or both.<sup>183</sup>

**Figure 6. 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. Although ramucirumab showed efficacy in patients with gastric cancer, experts thought it has only some potential to fulfill this need because survival was marginally increased and the benefits might not outweigh the increase in adverse events. Experts thought ramucirumab for treating gastric cancer would not be sufficient as monotherapy and most likely will be part of a combination therapy. 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.<sup>184-189</sup> We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** Noting the limited response to chemotherapy and lack of options for gastric cancer treatments, experts agreed that an unmet need exists and ramucirumab has potential to address this unmet need. However, combination ramucirumab and chemotherapy as second-line treatment was associated with severe adverse events, and experts pointed out that survival was increased by only a few months. In contrast, a clinical expert suggested that as monotherapy, ramucirumab could be an alternative for patients who cannot tolerate the side effects of doublet and triplet chemotherapy.<sup>187</sup>

**Acceptance and adoption:** Experts anticipate that both physicians and patients will adopt ramucirumab for treating gastric cancer, because second-line alternatives are very limited; they thought it would most likely be adopted as combination therapy. Patients will probably accept ramucirumab because it would be the only alternative with potential to extend overall survival. However, an expert remarked that elderly patients might not consider the potential of an overall survival extension of a couple months to be worth the possible side effects of ramucirumab.

**Health care delivery infrastructure and patient management:** Experts do not anticipate any change in health care delivery and infrastructure. They thought ramucirumab could be easily integrated into clinical care at cancer centers IV infusion clinics. Patient management is also expected to be unaffected. An expert with a research perspective anticipates that monitoring patients for adverse events, particularly hypertension, will be important.<sup>185</sup>

**Health disparities:** Experts thought that ramucirumab-associated disparities would be similar to other antibody-based therapies: its expense would make it out of reach for uninsured patients or middle- and low-income patients with high copayments. Being a new treatment for a cancer that has limited second-line options, experts anticipated that third-party payers would include ramucirumab in their formularies for labeled indications.

## **Hematologic Malignancy Interventions**



## 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 are derived from both B cells and T cells; however, the majority are of B-cell origin. Treatment of B-cell NHLs has improved in recent years with optimization of chemotherapy regimens and the introduction of 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 that inhibits Bruton's tyrosine kinase (Btk), a nonreceptor tyrosine kinase that plays multiple roles in the regulation of B lymphocytes. Proliferation and survival of malignant B cells may be driven by chronic signaling through the B-cell receptor, which activates multiple 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.<sup>190</sup> 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. Pharmacologic inhibition of 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 the inhibition of these pathways.<sup>191,192</sup>

Idelalisib (Zydelig®) is a first-in-class, orally administered, small-molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta.<sup>193,194</sup> 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.<sup>190</sup> 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.<sup>195,196</sup>

**Clinical trials:** Investigators have reported results from multiple trials of ibrutinib and idelalisib in treating patients with 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.<sup>197</sup>

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.<sup>198</sup> Importantly, both ibrutinib trials in patients with CLL demonstrated equivalent response rates in patients with or without a 17p deletion.<sup>197,198</sup>

More recently, researchers published results from the first randomized controlled trial of ibrutinib in patients with CLL, the RESONATE trial. This open-label 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).<sup>199</sup> 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).<sup>200</sup>

For patients with mantle cell lymphoma, data from a single-arm, open-label trial of ibrutinib (560 mg, once daily) in 111 patients with relapsed or refractory disease, Wang and colleagues reported an overall response rate of 68% (21% complete response, 47% partial response).<sup>201</sup>

In clinical trials, ibrutinib was reported as being well tolerated, with the majority of adverse events being of mild-to-moderate severity.<sup>197,198,200</sup> According to ibrutinib's prescribing information, common adverse events reported in patients with mantle cell lymphoma included abdominal pain, anemia, bruising, constipation, decreased appetite, diarrhea, dyspnea, fatigue, musculoskeletal pain, nausea, neutropenia, peripheral edema, rash, thrombocytopenia, upper respiratory tract infection, and vomiting. Common adverse events reported in patients with CLL included anemia, diarrhea, fatigue, musculoskeletal pain, nausea, neutropenia, pyrexia, rash, thrombocytopenia, and upper respiratory tract infection.<sup>202</sup>

Regarding idelalisib, investigators published results in 2014 from a randomized, double-blind, placebo-controlled trial of patients with relapsed/refractory CLL.<sup>203</sup> 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.

Investigators also published results in 2014 from a trial of idelalisib in patients with relapsed/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).<sup>204</sup> 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.<sup>203,204</sup> Frequent adverse events associated with idelalisib monotherapy included cough, diarrhea, dyspnea, fatigue, pneumonia, fever, and rash.<sup>204</sup> 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.<sup>203</sup> 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.<sup>205</sup>

**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. FDA has granted ibrutinib breakthrough therapy designation for three indications: (1) CLL harboring a 17p deletion, (2) relapsed/refractory mantle cell lymphoma, and (3) Waldenström's macroglobulinemia.<sup>206</sup> In November 2013, FDA granted accelerated approval for use of the drug in treating patients with mantle cell lymphoma who have received at least one prior therapy.<sup>207</sup> A second accelerated approval for use of the drug in treating patients with CLL who have received at least one prior therapy followed in February 2014.<sup>208</sup> In July 2014, FDA converted ibrutinib's approval in 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.<sup>209</sup> Before these approvals, FDA had granted ibrutinib breakthrough therapy designations for CLL harboring a 17p deletion and relapsed/refractory mantle cell lymphoma.<sup>206</sup> Additionally, FDA had granted ibrutinib a breakthrough therapy designation for treating Waldenström's macroglobulinemia, an indication for which Pharmacyclics and Janssen submitted a supplemental NDA in October 2014.<sup>206,210</sup>

Idelalisib was developed by Gilead Sciences, Inc., Foster City, CA. In July 2014, FDA approved marketing of idelalisib for three types of relapsed/refractory NHL: CLL, small lymphocytic lymphoma, and follicular lymphoma.<sup>211</sup> Before these approvals, FDA had granted idelalisib breakthrough therapy status for treating patients with CLL.<sup>212</sup>

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.

**Diffusion and cost:** As of the second quarter of 2014 (approximately 7 months after approval for mantle cell lymphoma and approximately 4 months after approval for CLL), Pharmacyclics estimated that ibrutinib was being used in approximately 40% of patients undergoing treatment for relapsed/refractory mantle cell lymphoma and in approximately 36% of patients undergoing treatment for relapsed/refractory CLL.<sup>213</sup> Ibrutinib is taken on an ongoing basis until disease progression or unacceptable toxicity. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, the average retail price for 1 month of ibrutinib at the recommended dose for mantle cell lymphoma (560 mg, once daily) and CLL (420 mg, once daily) is \$11,771 and \$8,830, respectively.<sup>214</sup> Patients take the drug until disease progression or unacceptable toxicity. In clinical trials in treating CLL and mantle cell lymphoma, patients received ibrutinib treatment for a median of about 9 months;<sup>200,201</sup> however, many patients were still taking ibrutinib at the cutoff for data analysis and the real-world duration of treatment has not been established.

At the end of idelalisib's first quarter of commercial availability, Gilead reported that the drug was being used in approximately 350 patients.<sup>215</sup> GoodRx listed an average retail price of \$3,773 for thirty 150-mg idelalisib tablets.<sup>216</sup> At a recommended dose of 150 mg twice daily, this represents a cost of approximately \$7,500 per month.<sup>205</sup> 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.<sup>205,217</sup>

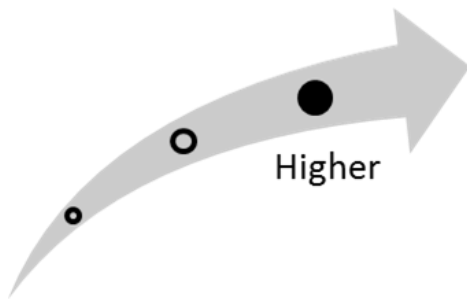
Searches of 11 representative, private, third-party payers that publish their policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA,

HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified policies regarding ibrutinib that cover the drug according to labeled indications when certain conditions are met.<sup>218,219,220-225</sup> 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 relapsed/refractory NHLs include bortezomib and lenalidomide for mantle cell lymphoma and alemtuzumab, lenalidomide, obinutuzumab, and ofatumumab for CLL.<sup>226</sup> Ibrutinib and idelalisib would represent additional treatment options for patients with relapsed B-cell NHL or certain high-risk patients with previously untreated NHL (e.g., patients with CLL harboring a chromosome 17 deletion).

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



Overall, experts commenting on these interventions opined 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 believe that the relatively benign side-effect profile of ibrutinib and idelalisib and their potential to be used in treating 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,<sup>227-232</sup> and six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating mantle cell lymphoma.<sup>233-238</sup> We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** A moderate to high unmet need for new treatments for CLL and mantle cell lymphoma was seen by the majority of experts commenting. They cited the propensity of these malignancies to recur and the lack of effective treatment options for patients with relapsed disease. However, multiple commenters also noted that the relatively small number of

patients affected by the diseases (particularly mantle cell lymphoma) limited the magnitude of the unmet need.

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 impact on patient health. One clinical expert who thought ibrutinib's potential to improve patient health was high noted the significant unmet need presented by high-risk patients whose disease harbors a chromosome 17 deletion and the preliminary evidence of ibrutinib's efficacy in this patient population.<sup>231</sup>

**Acceptance and adoption:** Both clinicians and patients were seen by commenters as highly likely to adopt the use of ibrutinib. Factors encouraging adoption included the limited treatment options for patients with relapsed 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. This would be primarily an issue for the uninsured, and those with high copayments, as commenters thought that payers would be likely to cover the drug once it is approved.

## Idelalisib

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of idelalisib for treating CLL,<sup>239-244</sup> and six experts, with similar backgrounds, offered perspectives on the topic of idelalisib for treating indolent NHL.<sup>245-250</sup>

**Unmet need and health outcomes:** A moderate unmet need exists in CLL and indolent NHL treatment according to the majority of experts who commented; they cited the fact that treatments for these conditions are rarely curative and that options for patients with relapsed/refractory disease have limited efficacy. One clinical expert suggested that patients intolerant of intensive chemotherapy (e.g., elderly patients, patients with coexisting conditions) had few available treatment options.<sup>242</sup> Commenters who thought the unmet need was small cited the range of available therapies used in treating B-cell lymphomas and noted that idelalisib was being used as an adjunctive therapy to rituximab in the largest clinical trial of the drug reported to date. One clinical commenter suggested that the availability of ibrutinib limits the magnitude of the unmet need in treating CLL; however, this commenter also noted that differences between the drugs are likely to render them each more efficacious in certain contexts.<sup>243</sup>

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 logical mechanism of action. Underscoring the preliminary nature of the data, one commenter with a clinical perspective suggested that initial data indicated limited accumulating toxicity with long-term exposure to idelalisib while also suggesting that the long-term effects of

PI3K inhibition by idelalisib would need to be examined in further trials.<sup>248</sup> Commenters who suggested that idelalisib has only minimal potential to improve patient health cited the preliminary nature of the data and that this left them unsure of the ultimate clinical benefit provided by the drug.

**Acceptance and adoption:** Both physicians and patients would likely widely adopt idelalisib, the experts thought, given limited treatment alternatives, ease of oral administration, and preliminary data indicating promising signs of efficacy. Experts who envisioned less widespread adoption again cited the preliminary nature of the data and suggested that some physicians and patients would await further data before opting for idelalisib treatment. Additionally, experts envisioned a high cost for idelalisib, which could place a financial burden on patients and cause them to opt for treatment alternatives.

**Health system infrastructure and staffing:** As an orally administered drug, idelalisib is unlikely to cause much if any change in health care system infrastructure and staffing, according to experts. A few experts suggested that displacement of certain intravenously administered CLL and indolent NHL treatments by idelalisib could cause a shift of patient care out of infusion centers; however, this was seen as only a minor disruption to the health care system.

**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. Some commenters thought that efficacy of this drug was still uncertain enough that they were unsure about the likelihood for coverage by insurance.

## 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.<sup>251,252</sup> Patients with high-risk polycythemia vera are typically treated with a form of cytoreductive therapy with the aim of preventing and managing thrombotic and bleeding complications; controlling symptoms; and minimizing risk of progression to more aggressive diseases (e.g., post-polycythemia vera myelofibrosis, acute myeloid leukemia).<sup>253</sup> First-line treatment of high-risk polycythemia vera is typically hydroxyurea; however, for patients whose disease is not adequately controlled by hydroxyurea or patients who are intolerant of the treatment, a substantial unmet need exists for safe and effective therapies.<sup>254</sup>

**Intervention:** 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.<sup>255</sup> 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).<sup>253</sup> 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.<sup>254</sup> 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.<sup>256,257</sup> 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, immunomodulatory drug, 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 ( $p<0.0001$ ).<sup>256</sup>

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 treatment with 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 ( $p=0.139$ ).<sup>257</sup>

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.<sup>258</sup>

**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.<sup>259</sup>

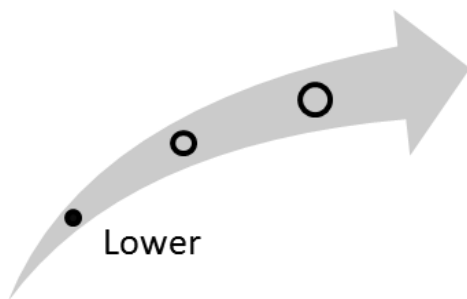
FDA approved ruxolitinib in 2012 for treating intermediate- or high-risk myelofibrosis, a myeloproliferative neoplasm related to polycythemia vera.<sup>258</sup> In June 2014, Incyte submitted a supplemental new drug application (sNDA) to FDA, seeking a label expansion to include treating patients with polycythemia vera who have had an inadequate response to hydroxyurea or cannot tolerate it (the patient population enrolled in the RESPONSE trial).<sup>260</sup> In December 2014, FDA approved ruxolitinib for treating “polycythemia vera patients who have an inadequate response to or cannot tolerate hydroxyurea.”<sup>261</sup>

**Diffusion and cost:** FDA only recently approved ruxolitinib for treating patients with polycythemia vera; however, ruxolitinib had previously received FDA approval as a treatment for patients with myelofibrosis.<sup>258</sup> Therefore, some off-label use of ruxolitinib in patients with polycythemia vera may have occurred before approval for this indication. A U.S.-based online aggregator of prescription-drug prices, GoodRx, listed prices for ruxolitinib (sixty 10 mg tablets as a 1-month supply) as between \$8,848 and \$10,035 (average \$9,321).<sup>262</sup> 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 \$112,000.

## Clinical Pathway at Point of This Intervention

In treating patients who have polycythemia vera, physicians manage symptoms by using phlebotomy to maintain a hematocrit level of less than 45% and reduce risk of thrombosis by using aspirin. For patients with intermediate- to high-risk polycythemia vera, cytoreductive therapy may also be employed. 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-alpha. 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.<sup>253,254</sup>

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



Overall, experts believed 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 for patients with the condition. 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 potential for ruxolitinib, 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.<sup>263-267</sup> 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 lack of FDA-approved treatments prior to this treatment. In particular, one expert speaking from a clinical perspective 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.<sup>265</sup>

However, commenters were more divided 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.<sup>265,266</sup> Other commenters viewed the RESPONSE data less favorably, suggesting that the data indicated limited efficacy,<sup>263</sup> and multiple 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.<sup>265,266</sup> 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.<sup>263,267</sup> Additionally, one clinical expert suggested that required twice-daily dosing could lead to adherence issues in some patients.<sup>265</sup>

**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.<sup>265</sup>

**Health disparities:** Ruxolitinib has no potential to improve health disparities, according to experts commenting. Multiple commenters suggested that the high cost of ruxolitinib could exacerbate any 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 accumulation of nonclonal B cells.<sup>268</sup> Patients with multicentric Castleman's disease experience significant morbidity. Few treatment options are available, and relapses in this patient population are common.<sup>269</sup> Novel treatments are needed. The recent FDA approval of siltuximab (Sylvant™) makes available for the first time a medication indicated for treating patients who have multicentric Castleman's disease.

**Intervention:** Overproduction of the pleiotropic cytokine interleukin-6 (IL-6) has been implicated in the pathogenesis of Castleman's disease.<sup>269</sup> 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).<sup>270</sup> Based on these observations, researchers have hypothesized that blocking the activity of IL-6 could ameliorate the symptoms of Castleman's disease.<sup>270,271</sup>

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.<sup>271</sup> 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.<sup>272,273</sup>

**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.<sup>274</sup> 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.<sup>275</sup> 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-treated patients, despite patients receiving siltuximab for more than twice as long as patients receiving placebo (median 375 days vs. 152 days).<sup>274</sup> 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.<sup>272</sup> The most common adverse events that occurred at least 10% more often in patients receiving siltuximab than with placebo were pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection.<sup>275</sup>

**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."<sup>275,276</sup> The siltuximab BLA was reviewed under FDA's priority review program.<sup>276,277</sup>

**Diffusion and cost:** Siltuximab has only recently become available on the U.S. market. According to a November 2014 query of a U.S.-based, online aggregator of prescription-drug

prices, GoodRx, retail prices for 100 mg and 400 mg vials of siltuximab for infusion are about \$860 and \$3,600, respectively.<sup>278,279</sup> 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.<sup>275</sup>

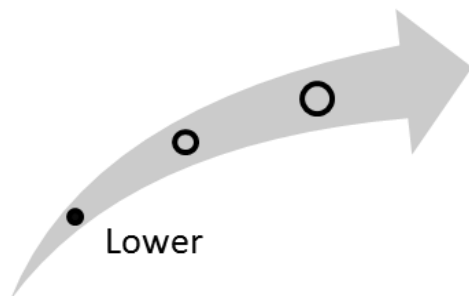
Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified three policies regarding siltuximab, which indicated that the drug is considered medically necessary for its FDA-approved indication.<sup>280-282</sup> Two of these policies require prior authorization for coverage.<sup>281,282</sup>

## Clinical Pathway at Point of This Intervention

Before siltuximab was approved, no therapies had been FDA approved for treating multicentric Castleman's disease; however, multiple systemic therapies have been used off label. These have included traditional cytotoxic chemotherapy regimens as well as more recent additions, such as the anti-CD20 monoclonal antibody rituximab and the immunomodulatory drug thalidomide.<sup>268,269</sup>

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.<sup>270</sup>

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



Overall, experts 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 eligible patient population 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.<sup>283-288</sup> 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 for treating 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

commenters universally 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 needs overall. The majority of experts commenting suggested that siltuximab has moderate potential to improve health in patients with multicentric Castleman's disease. Although commenters suggested that the phase II trial results that led to FDA approval were promising in terms of response rate and limited toxicity, they also noted the preliminary nature of these data. Experts noted that siltuximab does not represent a cure for multicentric Castleman's disease and, therefore, longer-term studies of the treatment's impact on patient outcomes and quality of life are needed.

**Acceptance and adoption:** Siltuximab is likely to achieve moderate to wide adoption by clinicians and patients, experts thought. They noted that lack of viable alternatives, the relatively low levels of toxicity associated with treatment, and the familiar mode of IV infusion as factors promoting clinician adoption. However, several experts suggested that cost might be a barrier for some patients and noted the need for ongoing infusions every 3 weeks.<sup>283,284,286</sup> Additionally, one clinical expert suggested that the potential for hypersensitivity reactions, which could require hospitalization, could dissuade some patients.<sup>286</sup>

**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 already are likely to have 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:** Siltuximab cost information was not available to experts at the time they commented. Even in the absence of this information, the consensus among commenters was that siltuximab would likely be expensive, as is seen with similar specialty pharmaceuticals for orphan diseases. The anticipated per-infusion cost, combined with the need to receive the infusions for an extended period of time, led commenters to conclude that adoption of siltuximab would increase the cost of care for this patient population. As a result, this new therapy may exacerbate health disparities between the uninsured or underinsured because it may be unaffordable to patients with limited economic means.

## **Prostate Cancer Intervention**

## Radium-223 Dichloride (Xofigo) for Treatment of Solid Tumor Bone Metastases

**Unmet need:** Many cancers, in particular breast, prostate, and lung cancers, metastasize to bone, where they can cause chronic pain and skeletal-related events (e.g., fractures) that can adversely affect both patient quality of life and survival.<sup>289</sup> Current treatments targeting bone metastases are largely palliative, providing pain relief or delaying skeletal-related events without having significant effects on overall disease progression or patient survival.

These treatment options include the radionuclides strontium-89 and samarium-153-EDTMP (ethylenediamine tetra [methylene phosphonic acid]). These are radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases.<sup>289</sup> Preferential accumulation of the radioactive compound purportedly concentrates the radiation dose at the target bone metastases. Although available radionuclides have shown some efficacy in relieving bone pain, the type of radiation that they emit penetrates tissues deeply enough to harm bone marrow, which limits the deliverable dose, enabling palliation of only one symptom.<sup>290</sup>

**Intervention:** Radium-223 dichloride (Xofigo<sup>®</sup>) is a novel bone metastasis–targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than the radiation generated by available radiopharmaceuticals indicated for treating bone metastases.<sup>291</sup> This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes.<sup>291</sup> Radium-223 dichloride is administered intravenously at a dosage of 50 kilobecquerel (1.35 microcurie)/kg, once every 4 weeks, for up to six treatment cycles.<sup>292</sup>

**Clinical trials:** In July 2013, results were published from a double-blind, randomized controlled trial of the radiopharmaceutical versus placebo in 921 patients with castration-resistant prostate cancer (CRPC) and skeletal metastases who were ineligible for initial or further treatment with docetaxel.<sup>293</sup> In this trial, radium-223 dichloride was reported to have increased overall survival by 3.6 months compared with survival with placebo, representing a 30% reduction in the risk of death ( $p=0.001$ ). This represents the first time a radiopharmaceutical agent intended to treat prostate cancer bone metastases demonstrated an increase in overall survival. Radium-223 dichloride treatment also prolonged the time to first skeletal-related event by 5.8 months compared with placebo (15.6 months vs. 9.8 months; HR, 0.66;  $p<0.001$ ).<sup>293</sup>

Radium-223 dichloride treatment was reported as being well tolerated by patients; the most significant adverse event was myelosuppression. Rates of grade 3 or 4 neutropenia were 2.2% in the radium-223 dichloride arm and 0.7% in the placebo arm, and rates of grade 3 or 4 thrombocytopenia were 6.3% in the radium-223 dichloride arm and 2% in the placebo arm.<sup>294</sup> Other commonly reported adverse events were similar between groups (bone pain, constipation, diarrhea, nausea, and vomiting).<sup>293</sup> The relatively benign adverse-event profile of radium-223 dichloride treatment may allow its use in combination with other cancer treatments. For example, investigators have initiated a phase III clinical trial testing the combination of radium-223 and the androgen-synthesis inhibitor abiraterone in patients with bone-predominant, asymptomatic, CRPC.<sup>295</sup>

**Manufacturer and regulatory status:** Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany, developed radium-223 dichloride. In March 2014, Bayer acquired Algeta.<sup>296</sup> FDA approved radium-223 dichloride in May 2013, three months ahead of the expected decision date. It is indicated for treating patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease.<sup>292,297</sup> Before the approval, FDA had granted radium-223 dichloride fast-track status for treating CRPC with bone metastases.<sup>298</sup>

**Diffusion and cost:** The wholesale cost of radium-223 dichloride is reportedly \$11,500 per injection (\$69,000 for a full course of 6 injections).<sup>299</sup> The U.S. Nuclear Regulatory Commission

has cleared distribution of radium-223 dichloride; individual sites must be licensed to administer the drug.<sup>299</sup> In the second quarter of 2014, the manufacturer reported worldwide sales of radium-223 as €43 million (approximately \$53 million at November 2014 exchange rates); however, the report did not break out sales by geographic region.<sup>300</sup> A survey of U.S. medical oncologists performed about 1 year after radium-223 became available in the U.S. market indicated that about two-thirds of survey respondents had prescribed radium-223. Among physicians who had prescribed radium-223, about one-third had prescribed it in combination with another metastatic CRPC therapeutic agent (e.g., abiraterone).<sup>301</sup>

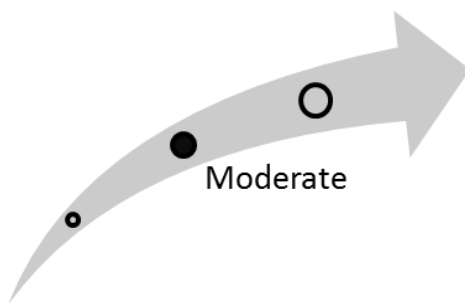
A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 7 payers with policies for radium-223 dichloride specifying that they cover the treatment for patients with bone metastases from CRPC.<sup>302-308</sup> Most policies require prior authorization and may require that the patients' bone metastases be symptomatic and that the patient have no known visceral metastases.

Radium-223 dichloride is also under investigation for treating osteosarcoma and breast cancers with bone metastases.<sup>309,310</sup>

## Clinical Pathway at Point of This Intervention

Patients with cancer that has metastasized to bone are typically treated with a combination of locoregional treatments, systemic therapies, and pain medications.<sup>289</sup> Palliative local treatments include external beam radiation therapy, MR-guided focused ultrasound ablation, and surgical resection.<sup>311</sup> Systemic treatments include chemotherapy, hormone therapy, and modulators of bone remodeling such as bisphosphonates and the RANKL antibody denosumab.<sup>312</sup> Additional systemic agents that are targeted to bone include radiopharmaceuticals such as strontium-89 and samarium-153-EDTMP, which preferentially accumulate in sites of bone metastasis and expose the cancer cells to beta and/or gamma radiation.<sup>289</sup> Radium-223 dichloride represents a novel, systemic radionuclide as the first alpha particle–emitting radionuclide indicated for treating this condition.

**Figure 10. Overall high-impact potential: radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases**



Overall, experts commenting on this topic thought that radium-223 dichloride has significant potential to improve current treatments for bone metastases pain, particularly for patients with prostate cancer bone metastases. Although experts saw significant potential for wide adoption, the similar nature of this agent to other treatments suggested to experts that radium-223 dichloride would have a limited impact on health care system infrastructure and practices. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

## Results and Discussion of Comments

Seven experts, with clinical, research, clinical engineering, and health systems backgrounds, offered perspectives on this intervention.<sup>313-319</sup> We have organized the following discussion of expert comments according to the parameters on which they commented.

**Unmet need and health outcomes:** The need for improved treatments for bone metastases is moderately or very important, the experts thought, citing the high prevalence and significant impact on patient quality of life and survival. Most experts suggested that the compound's purported improved safety profile relative to existing radiopharmaceutical treatments for bone metastases represents a significant improvement. However, one expert with a research perspective, who thought the unmet need addressed by radium-223 dichloride was small, suggested that the compound represents only an incremental improvement.<sup>319</sup>

Radium-223 dichloride has moderate to large potential to improve patient health, the experts thought, citing the increased overall survival time reported in the recently completed phase III trial and the relatively benign toxicity profile thus far. Several experts noted the ability of radium-223 dichloride to improve patient quality of life (e.g., lessening pain) in addition to its effects on survival and disease progression.

One clinical expert expressed caution regarding the potential for long-term sequelae of radium-223 dichloride, noting that use of another radium isotope (radium-224) in treating ankylosing spondylitis had led to an increase in leukemia incidence in treated patients. However, the expert also noted that the two radium isotopes have differing decay patterns (which could alter the systemic radiation exposure) and that such long-term sequelae may not be as relevant to patient populations with metastatic disease whose long-term prognosis is relatively poor.<sup>313</sup>

**Acceptance and adoption:** In line with their view that radium-223 dichloride has significant potential to improve health outcomes, most of the experts thought the treatment would be widely adopted. Experts cited its reported efficacy, safety, relatively benign adverse-event profile, ease of use, and routine administration as factors that would enhance adoption. One expert with a clinical engineering perspective suggested that a small proportion of patients might hesitate to accept treatment involving a radioactive isotope; however, this expert thought that overall, radium-223 dichloride is likely to be widely accepted by patients.<sup>314</sup>

Radium-223 dichloride would likely be priced at a premium over other radiotherapy options, the experts suggested, and a majority indicated that it would increase the overall cost of care. This could slow adoption, multiple experts suggested, adding that payers might require stepped therapy.

**Health care delivery infrastructure and patient management:** Experts did not think that using radium-223 dichloride would require significant changes to health care delivery and infrastructure or patient management, noting the similarity between radium-223 dichloride treatment methods and radiopharmaceuticals now used.

**Health disparities:** Generally, experts did not think radium-223 dichloride would significantly shift health disparities. A few experts noted that the cost relative to existing palliative treatments would make the treatment prohibitive for patients without insurance or insured patients with limited financial resources and high copayments, potentially worsening health disparities. Conversely, one expert with a clinical perspective suggested that underserved populations might present with more advanced disease and therefore, radium-223 dichloride might have a larger impact in an underserved population.<sup>313</sup>



## **Skin Cancer Interventions**

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

**Unmet need:** Despite recent advances treatment options for melanoma, many patients in whom advanced melanoma has been diagnosed have a poor prognosis and additional new treatments are needed. Recent phase III clinical trials with the anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody, ipilimumab (Yervoy<sup>®</sup>), demonstrated the potential of immune system checkpoint inhibitors to produce durable responses in patients with advanced melanoma by activating the body's immune system.<sup>320,321</sup> However, only a small minority of patients experience such a response, and new approaches to stimulate immune responses to melanoma are highly sought. One approach targets the programmed death-1 (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<sup>®</sup>) and pembrolizumab (Keytruda<sup>®</sup>).<sup>322-324</sup>

**Intervention:** Evading destruction by the body's immune system is a hallmark of cancer, and researchers have identified multiple mechanisms by which cancers induce immune tolerance.<sup>322,325</sup> One such mechanism is the co-option 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 anti-cancer immune response.<sup>322</sup>

PD-1 is a central player in one of these checkpoints.<sup>322</sup> 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.<sup>326</sup> 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.<sup>322</sup>

Nivolumab is a fully humanized, immunoglobulin G4 monoclonal antibody highly specific for PD-1.<sup>327</sup> 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.<sup>324</sup> 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.<sup>328</sup> 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.<sup>328</sup>

Nivolumab and pembrolizumab are administered by IV infusion. In phase I trials, researchers tested escalating doses of nivolumab in patients who have various cancers, infusing doses ranging from 0.3 to 10 mg/kg.<sup>328,329</sup> In ongoing phase III trials, patients with melanoma are treated with 3 mg/kg of nivolumab administered once every 2 weeks.<sup>330-333</sup> Pembrolizumab, which was recently FDA approved, has prescribing information recommending 2 mg/kg once every 3 weeks, and treatment may continue for up to 2 years.<sup>334,335</sup>

**Clinical trials:** Nivolumab and pembrolizumab are being tested primarily as immunotherapy for advanced melanoma and nonsmall cell lung cancer (NSCLC).<sup>331-333,336-343</sup> Additionally, investigators have initiated phase I trials of nivolumab and pembrolizumab for treating triple-negative breast cancer, head and neck cancer, urothelial tract cancer, gastric cancer, and blood cancers.<sup>328,329,344,345</sup>

Results from KEYNOTE-001, a phase I, open-label trial of 135 patients with advanced melanoma, were published in 2013. Investigators 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. Additionally, 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.<sup>346</sup>

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 (120 patients) or investigator's choice of chemotherapy (47 patients); the objective response rate was compared between both 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%).<sup>347</sup>

The efficacy of nivolumab 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 in November 2014 reporting that after 1 year of treatment of 418 patients with nivolumab, significant improvements were seen in overall survival and progression-free survival compared to dacarbazine. Overall survival in the nivolumab group was 73% (95% CI, 65% to 79%) and in the dacarbazine group 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.<sup>348</sup>

Additionally, in June 2014, the manufacturer announced 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.<sup>349</sup>

**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*<sup>V600</sup> mutation.<sup>350,351</sup> FDA granted nivolumab fast-track designation in 2013 for treating melanoma, NSCLC, and renal cell carcinoma.<sup>352</sup>

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 had progressed after treatment with ipilimumab or, if melanoma was *BRAF*<sup>V600</sup> mutation positive, a *BRAF* inhibitor.<sup>353</sup> 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.<sup>353,354</sup> FDA had earlier granted pembrolizumab breakthrough therapy status for treating advanced melanoma.<sup>355</sup>

**Diffusion and cost:** Because of the recency of the nivolumab approval, no cost information is available yet on the drug in the United States. However, 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. Therefore, a single infusion for a 70 kg patient at the typical dose of 3 mg/kg would cost approximately \$15,300 if costs were similar in the United States.<sup>356,357</sup> Bristol-Myers Squibb also manufactures the drug ipilimumab, a different immune-checkpoint antibody that is FDA approved for treating advanced melanoma. Ipilimumab has been reported to cost about \$6,800 for one 50 mg vial.<sup>358</sup> If administered at a dose of 3 mg/kg in a 70 kg patient, this amounts to a cost of about \$30,000 per infusion. Therefore, it is likely that nivolumab will be priced within this range in the United States.

Shortly after FDA approved pembrolizumab, Merck announced the drug would cost about \$12,500 per month, or \$150,000 per patient per year if patients remain on the therapy.<sup>359,360</sup> However, a U.S.-based, online aggregator of prescription-drug prices, GoodRx, listed costs as of October 2014 of about \$7,100 for three vials of 50 mg, which is roughly the amount (~150 mg) one patient would use for one treatment cycle.<sup>361</sup> Thus, actual pricing is lower than that stated in Merck's initial announcement. If a patient continued on treatment for a full year, the cost would be about \$120,700 (17 cycles at \$7,100 per cycle). The discrepancy between Merck's initial price and the cost reported by GoodRx could be attributed to the initial value of \$12,500 being an estimated price, which is similar to the average price of most innovative oncology drugs, whereas the GoodRx price is the actual acquisition price for pembrolizumab.<sup>362</sup>

To identify coverage policies, ECRI Institute routinely searches 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). We found no policies for nivolumab and pembrolizumab at these payers at this time, but they may not have updated their policies yet. Blue Cross/Blue Shield of Tennessee has a policy that considers pembrolizumab to be medically necessary for treating melanoma and will offer coverage if specific criteria are met.<sup>363</sup> Payers typically cover cancer drugs for their FDA-approved indications. Therefore, additional third-party payers will likely offer coverage. Pembrolizumab is available through a manufacturer-sponsored expanded-access program to select patients who do not have health insurance, or have health plans that do not cover pembrolizumab, or have coverage but cannot afford copayments.<sup>364</sup>

## Clinical Pathway at Point of This Intervention

For systemic treatment of advanced melanoma, three options exist: 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:<sup>365</sup>

- 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

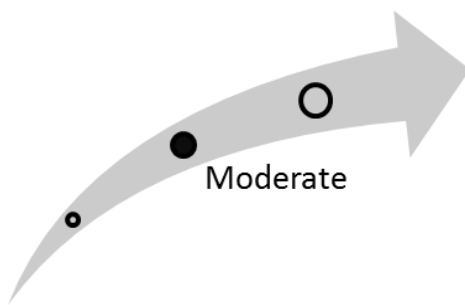
PD-1 checkpoint inhibitors have the potential to compete with existing treatments for advanced melanoma. In clinical trials, nivolumab and pembrolizumab have been and are being tested head-to-

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.<sup>322,330–333,366</sup> 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.<sup>367,368</sup>

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.<sup>323</sup> 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.<sup>369</sup>

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.<sup>322</sup> 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: PD-1 immune checkpoint inhibitors: nivolumab (Opdivo) and pembrolizumab (Keytruda) for treatment of advanced melanoma**



Nivolumab and pembrolizumab have moderate potential to address an unmet need for melanoma patients, 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 ipilimumab treatment. Because of the lack of options for this patient population, PD-1 inhibitors are expected to be adopted by both clinicians and patients, thought experts, and are not anticipated to 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,<sup>370–375</sup> and seven experts, with similar backgrounds, offered perspectives on the topic of pembrolizumab (which was earlier called lambrolizumab) for treating advanced melanoma.<sup>376–382</sup> 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 drugs 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 drugs, such as PD-1 inhibitors, are needed to close the gap for patients whose melanoma does not respond to current therapies. Additionally, this same group of experts also believes that efficacy data of nivolumab and pembrolizumab show potential to improve response rates and extend survival.<sup>374,375</sup> PD-1 antibodies could improve patient health and decrease the cost of standard therapies, was the opinion of an expert with research experience.<sup>375</sup>

**Acceptance and adoption:** Although a couple of experts were concerned that pembrolizumab would be adopted only if future 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.<sup>377,380</sup> Advanced melanoma progresses rapidly; thus, any drug capable of slowing progression of refractory disease will be accepted for treating melanoma, two clinical experts noted.<sup>374,381</sup>

**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 experts. Additionally, they do not anticipate much impact on patient management other than the fact that patients now have an option when ipilimumab stops working.<sup>374,378</sup> A clinical expert also thought that if sufficient efficacy data accumulate, pembrolizumab might displace ipilimumab as first-line therapy.<sup>379</sup>

**Health disparities:** Overall, PD-1 inhibitors are not expected to affect health disparities, although experts are concerned nivolumab and pembrolizumab will be costly and could increase health disparities in patients without insurance and even those with insurance, if the drug is more costly than existing options. 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, which would lead to a disproportionate number of patients from this group to receive PD-1 antibody treatment, opined a clinician.<sup>374</sup>

## 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 due to acquired drug resistance.<sup>383</sup> 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.<sup>384</sup>

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.<sup>385,386</sup> 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.<sup>385,386</sup> Additionally, 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.<sup>387</sup>

T-VEC purportedly 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.<sup>385,387</sup> 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.<sup>387,388</sup> GM-CSF encoded by the genetically modified virus purportedly enhances this systemic immune response by recruiting dendritic immune cells to the site(s) of viral infection.<sup>387</sup>

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.<sup>389</sup>

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.<sup>390,391</sup>

**Clinical trials:** T-VEC is being tested in injectable stage IIb, stage IIc, or stage IV melanoma that is not surgically resectable. Results from the phase III OPTiM/Study (NCT00769704) were presented at the 2014 American Society of Clinical Oncology Annual Meeting, which evaluated

durable response rates and overall survival in 436 patients with advanced melanoma.<sup>390,392</sup> 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). Additional 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.<sup>392</sup>

**Manufacturer and regulatory status:** T-VEC was developed by BioVex Group, Inc., Woburn, MA; BioVex was acquired by Amgen, Inc., Thousand Oaks, CA, in January 2011.<sup>393</sup> A phase III trial of T-VEC in patients with advanced melanoma, the III OPTiM/Study (NCT00769704), has been completed. Amgen filed with FDA for regulatory approval in July 2014 on the basis of data from the OPTiM/Study.<sup>395-397</sup>

If approved, T-VEC would be indicated for adult patients 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.<sup>390</sup> Patients with bone or cerebral metastases would be ineligible for T-VEC treatment. A phase I/II trial is investigating combination therapy with T-VEC and ipilimumab in patients with treatment-naïve, advanced melanomas that are ineligible for curative surgical resection.<sup>398</sup> Potential 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, 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. Additionally, storing and handling this agent will require additional precautionary measures.<sup>399</sup> Costs of other oncologic immunotherapy, such as Provenge for treating prostate cancer, are between \$90,000 and \$100,000 per patient per regimen. Should ipilimumab eventually be approved as part of combination therapy with T-VEC, treatment costs would further increase.

Because T-VEC is not yet approved by FDA, no coverage, coding, or payment information is available. As an injected medication administered in the 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 and vemurafenib) for the labeled indications.<sup>400-408</sup>

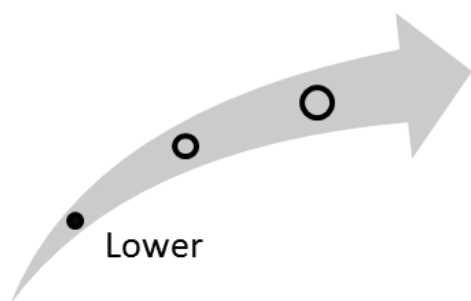
## Clinical Pathway at Point of This Intervention

Patients with disseminated or unresectable or metastatic melanoma are typically treated with one of a number of systemic therapies and/or radiation therapy.<sup>409</sup> 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 be a complementary intervention to 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 and pembrolizumab). Two early phase clinical trials—testing T-VEC plus ipilimumab and T-VEC plus pembrolizumab—are ongoing.<sup>410,411</sup>



**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. Although a clinical expert concurred with the opinion that T-VEC can address an unmet need, this expert also believes its 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.<sup>412-417</sup> 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 quality of life and extend their survival, all experts agreed. Most thought evidence demonstrating T-VEC's efficacy for treating melanoma is insufficient. However, experts believe 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 being statistically significant, T-VEC is a potential novel option that could improve benefits if used in combination with other melanoma treatments, two experts discussed.<sup>414,415</sup>

**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 relative 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.<sup>414</sup>

**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 therapeutic. Even with insurance coverage, co-pays could be high and unaffordable to some patients.

## **Thyroid Cancer Intervention**

## Multikinase Inhibitors: Sorafenib (Nexavar) and Lenvatinib (E7080) 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.<sup>418</sup> 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 (about 15% of cases), prognosis worsens significantly. Recurrent disease, particularly metastatic disease, is frequently less responsive to radioactive iodine, and patients have a poor prognosis and limited treatment options.<sup>418,419</sup> Until recently, treatment options for patients with advanced, RAI-refractory disease were limited to surgery, radiation therapy, and pharmacologic suppression of thyroid-stimulating hormone. FDA recently approved sorafenib (Nexavar®) for this patient population;<sup>419,420</sup> however, its response rate can be as low as 12%. Therefore, additional interventions are needed for patients whose disease does not respond to sorafenib. Lenvatinib is another multikinase inhibitor that could provide an alternative approach for treating patients who have locally advanced or metastatic, RAI-refractory thyroid cancer.<sup>421</sup>

**Intervention:** Sorafenib and lenvatinib are oral, small molecule drugs with broad specificity for a range of tyrosine kinases that modulate angiogenesis and tumor cell proliferation and survival.<sup>421,422</sup> 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 mitogen-activated protein (MAP) kinase pathway.<sup>421,423</sup> By binding and inhibiting the kinase activity of these molecular targets, sorafenib and lenvatinib 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*<sup>V600</sup> 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.<sup>423-426</sup> 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.<sup>421</sup>

In late-phase clinical trials, patients with locally advanced or metastatic, RAI-refractory differentiated thyroid cancers were treated with 400 mg of orally administered sorafenib twice daily (identical to the dosing established for FDA-approved sorafenib indications) or orally administered lenvatinib at a daily dose of 24 mg.<sup>427-429</sup> Prescribing information for sorafenib 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.<sup>427</sup>

**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.<sup>418</sup> Therefore, researchers undertook two phase III trials, DECISION and SELECT, to assess the efficacy of sorafenib and lenvatinib, respectively, compared with placebo in patients with progressive, RAI-refractory, differentiated thyroid cancer.<sup>428,429</sup>

At the 2013 American Society of Clinical Oncology Annual Meeting, Brose and colleagues reported that out of 417 patients, those in the sorafenib arm (400 mg, twice daily) of the DECISION trial demonstrated a significant increase the primary endpoint of progression-free survival (10.8 months vs. 5.8 months; HR 0.58;  $p < 0.0001$ ).<sup>430</sup> There was no significant difference 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.<sup>430,431</sup> Two deaths during the trial, one in each study arm, were attributed to the study drug.<sup>430</sup> These findings were replicated in preliminary studies in patients with advanced follicular and papillary thyroid carcinomas.<sup>432</sup>

Mid-stage trials sponsored by the Memorial Sloan-Kettering Cancer Center (New York, NY) are investigating combination therapy with sorafenib and everolimus or temsirolimus (inhibitors of mammalian target of rapamycin, or mTOR) for treating thyroid cancer.<sup>433,434</sup> Additionally, the National Cancer Institute is sponsoring mid-stage trials of sorafenib in patients with medullary thyroid cancer,<sup>435</sup> as well as in young patients (aged 2–21 years) with papillary thyroid cancer.<sup>436</sup> Additional studies of sorafenib are ongoing in multiple solid tumor types, including a manufacturer-sponsored, phase III study in patients with breast cancer.<sup>437,438</sup>

Schlumberger and collaborators presented results from the SELECT trial at the 2014 American Society of Clinical Oncology Annual Meeting. 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;  $p < 0.0001$ ). At the time of the analysis, overall survival had not been reached and the most common grade 3–4 lenvatinib-related adverse events were appetite decrease, diarrhea, hypertension, proteinuria, and weight loss. Due to adverse events, the initial dose of 24 mg per day was reduced in 78.5% of patients and discontinued in 14.2% of patients.<sup>439</sup>

**Manufacturer and regulatory status:** Sorafenib was developed by Bayer AG, Leverkusen, Germany, in collaboration with Onyx Pharmaceuticals, Inc., now a subsidiary of Amgen, Inc., Thousand Oaks, CA. Basing its decision on data from the phase III DECISION trial, FDA approved sorafenib for treating RAI-refractory thyroid cancer, in November 2013.<sup>440,441</sup> Furthermore, between June and July 2014, Bayer received approval for use of sorafenib for treating RAI-refractory thyroid cancer in Canada, the European Union, and Japan.<sup>442–444</sup> 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.<sup>427,445</sup>

Lenvatinib is being developed by Eisai, Inc., Tokyo, Japan. FDA granted lenvatinib orphan drug status for treating RAI-refractory thyroid cancer, in December 2012.<sup>446,447</sup> In August 2014, Eisai announced that it had submitted marketing approval applications for lenvatinib in both the United States and Europe.<sup>448</sup> In October 2014, FDA assigned priority review to the lenvatinib NDA, and the decision deadline under the Prescription Drug User Fee Act is April 14, 2015.<sup>449</sup>

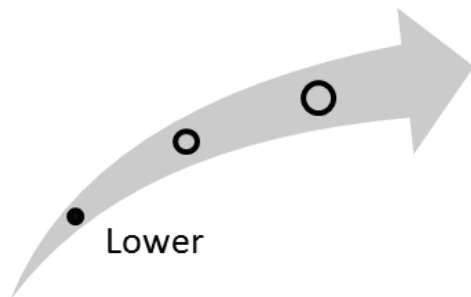
**Diffusion and cost:** For sorafenib, an October 2014 query of a U.S.-based, online aggregator of prescription-drug prices, GoodRx, found that at the clinical dose of 400 mg twice daily, treatment would cost about \$11,600 per month.<sup>450</sup> Sorafenib use may significantly add to the cost of care for patients with advanced, RAI-refractory thyroid cancers. Several third-party payers had established coverage policies for off-label use of sorafenib in treating differentiated thyroid cancer. Among 11 representative, private, third-party payers that publish their coverage policies online, 4 had policies specific to coverage of sorafenib.<sup>451–454</sup> The manufacturers offer several financial-assistance options through REACH<sup>®</sup>, a patient-assistance program for patients prescribed sorafenib.<sup>455</sup>

No cost information is available yet in the United States for lenvatinib, but it will likely have a similar price to sorafenib.

## 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.<sup>419</sup> Several systemic therapies have been studied for treating patients who have differentiated thyroid cancer that is not amenable to surgery and is not responsive to RAI. 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. Sorafenib is the only FDA-approved multikinase for treating locally recurrent or metastatic, progressive, RAI-refractory thyroid cancer; it is considered standard therapy. If approved, lenvatinib also has potential to be incorporated in the clinical pathway.<sup>456</sup> Another possible competitor of sorafenib and lenvatinib, sunitinib, is under examination in ongoing late-stage trials. Sunitinib is commercially available and could be prescribed off label.<sup>457,458</sup>

**Figure 13. Overall high-impact potential: multikinase inhibitors: sorafenib (Nexavar) and lenvatinib (E7080) for treatment of differentiated thyroid cancer**



Although they do not provide a complete cure, sorafenib and lenvatinib are capable of partially treating and stabilizing RAI-refractory thyroid cancer, as demonstrated by clinical results, opined three experts commenting on these interventions. Basing their opinions on improved progression-free survival data, most of the experts considered sorafenib and lenvatinib to have potential to improve outcomes in patients. A head-to-head comparison between the two drugs has not been performed, two clinicians noted; such studies could help determine which agent would benefit patients more. Another expert 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. 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 sorafenib for treating differentiated thyroid cancer,<sup>459-464</sup> and six experts, with similar backgrounds, offered perspectives on the topic of lenvatinib for treating differentiated thyroid cancer.<sup>465-470</sup> 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 sorafenib and lenvatinib was seen by experts as having moderate

importance, which could be limited by the relatively small patient population affected. 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. Even though sorafenib is used for treating RAI-refractory thyroid cancer, not all patients' disease responds, thus an unmet need exists for additional options. Lenvatinib could be a potential alternative to address the unmet need, most of the experts thought. Although they noted increased side effects and uncertainty about lenvatinib treatment duration, two clinicians considered the difference in progression-free survival to be impactful.<sup>467,470</sup>

**Acceptance and adoption:** For sorafenib for treating RAI-refractory thyroid cancer, experts anticipated moderate-to-wide physician and patient acceptance. Experts noted that as an oral medication, the drug should easily diffuse, especially because it is already approved and covered by insurance. Another clinician suggested sorafenib could eventually be used as first-line treatment in addition to second-line treatment.<sup>467,470</sup> Lenvatinib has moderate potential to be adopted by patients and clinicians, experts opined, due to limited treatment options and its oral administration and improved efficacy. However, one expert thought the added adverse events could be a barrier to acceptance.<sup>466</sup> Another clinical expert noted the full benefit of lenvatinib should be demonstrated in a clinical trial in which its efficacy is compared with sorafenib.

**Health system infrastructure and patient management:** 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.<sup>464</sup> Similar to sorafenib, the experts do not expect lenvatinib to disrupt health care delivery and patient management.

**Health disparities:** For sorafenib, even though it is an expensive drug, most experts think it 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. Experts anticipate that lenvatinib will be expensive as well and might cause health disparities, in particular with patients of low socioeconomic status with high copayments. If approved, lenvatinib is expected to cost about the same as sorafenib 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.. However, two experts expect the impact to be lower because of the small patient population.<sup>461,464</sup> Additionally, if sorafenib and lenvatinib continue to show efficacy in additional trials, it is possible that more insurance carriers will offer coverage.

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