FRONTIERS IN CARE
The Clinical Trial and the Patient’s Voice: “I’m Extremely Lucky to Be Alive”

Mary Caffrey

WESLEY HALL SOUNDS REMARKABLY calm for someone about to start his fourth course of cancer treatment. His conversation with Evidence-Based Oncology™ (EBO™) took place just after Thanksgiving, after Hall learned that his stage IV stomach cancer diagnosed in 2013 had metastasized to his liver.

At first, doctors feared the cancer had also spread to Hall’s spine and his rib, but that turned out to be a false alarm. “I was never so glad just to have liver cancer in my life,” Hall says with a laugh.

That positive outlook is hard won, for Hall has been on quite a journey. “I’m calm, because I’m extremely lucky to be alive,” Hall says. He credits oncologist Nuruddin Jooma, MD, MPH, and the team at Florida Cancer Specialists & Research Institute, with “not letting any grass grow under [my] feet,” and getting him into a clinical trial within weeks of diagnosis.

By December 19, 2017, Hall had started his third clinical trial in 4 years, and the second involving immunotherapy. He is among several dozen patients taking Lycera’s investigational oral agent LYC-55716, a ROR γ agonist that attacks the tumor in multiple ways. The therapy is described as a master switch, simultaneously regulating the activity of both Th17 (helper) T cells and Tc17 (cytotoxic) T cells; the manufacturer says the approach “both ‘removes the brake’ and ‘pushes on the accelerator’ of immune function.”

Mary Caffrey

INTERVIEW
Provocative Questions, Better Biomarkers, and the Prospect of Triple Therapy: A Conversation With NYU’s Jeffrey S. Weber, MD, PhD

Jeffrey S. Weber, MD, PhD

IT HAS BEEN MORE THAN 4 YEARS since The American Journal of Managed Care® first spoke with Jeffrey S. Weber, MD, PhD, about immunotherapy and specifically about ipilimumab (Yervoy, Bristol-Myers Squibb [BMS]). At the time, oncologists were still gaining an understanding of this class of cancer treatment, which activates the body’s own immune system by flipping the switches—or checkpoints—that regulate how the body attacks foreign cells and leaves healthy ones alone. Payers were coming to grips with the price: The drug cost $120,000 a year, an amount that would be eclipsed by combination therapy.

NEARLY 20 YEARS AFTER Genentech set a new standard for treatment of patients with breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2), the FDA approved Mylan and Biocon’s trastuzumab biosimilar MYL-14010 in December 2017, referenced on the drug trastuzumab (Herceptin). Mylan’s biosimilar, which will be marketed in the United States as Ogivri, will compete with 1 of the most profitable cancer therapies in the world: Herceptin’s global sales were reported to be $6.7 billion in 2016. A report in FiercePharma noted that Herceptin has 90% market share for HER2-positive breast cancer, which affects 15% to 20% of patients, and various sources listed the drug’s price at $64,000 to $70,000 a year in 2016.
If castration-resistant prostate cancer (CRPC) goes undetected in patients receiving ADT...

AN UNCONTROLLABLE THREAT MAY SOON EMERGE

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ADT = androgen-deprivation therapy; PSA = prostate-specific antigen.

*Estimated prevalence based on a dynamic progression model.

References:


In 2017, 106,505 men in the United States were estimated to have nonmetastatic CRPC.*

Ninety percent of men with nonmetastatic CRPC ultimately develop bone metastases, which can lead to pain, pathologic fractures, and spinal cord compression.2,3

Diligent tracking of PSA and PSA doubling time may help alert you to potential disease progression early on. To learn more about the risk of CRPC, visit RiskofRisingPSA.com

*Estimated prevalence based on a dynamic progression model.
If castration-resistant prostate cancer (CRPC) goes undetected in patients receiving ADT...

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Visit RiskofRisingPSA.com

KEEP YOUR EYES ON THE RISE
Use of biomarkers will become more important as the cost of immuno-therapy increases. Among recent developments, FDA has approved Foundation Medicine’s test for variants in 324 genes known to drive cancer.
**FROM THE CHAIRMAN**

**Immuno-Oncology Over the Long Haul**

**HENNESSY**

FOR THE LAST FEW YEARS, our February issue of Evidence-Based Oncology™ has offered perspectives on immuno-oncology—its promise, its cost, and the opportunity to enter once unimaginable frontiers. Indeed, 2017 has brought the breakthrough predicted a year ago: the approval of the first chimeric antigen receptor (CAR) T-cell therapy. Right now, there are only 2 FDA-approved treatments, each for a single indication, but ongoing work suggests more patients could be eligible for these treatments soon.

Science is only part of the story, however. The staggering sums for these treatments—the first approved CAR T-cell therapy cost $475,000—mean that a long-term discussion about how we pay for cancer treatment is inevitable. As Jeffrey Weber, MD, PhD, points out in an interview in this issue, CAR T-cell therapy may be getting the attention, but the prospect of triple combination therapy that costs just as much is very much on the minds of oncologists. The challenge of drug prices even made headlines during President Trump’s recent State of the Union address.

**CAR T-cell therapy may be getting the attention, but the prospect of triple combination therapy that costs just as much is very much on the minds of oncologists, as Jeffrey S. Weber, MD, PhD, points out in this issue.**

Dr Weber notes that an important aspect of this issue is making sure that expensive treatments reach the right patients, and he’s pleased to see support from the National Cancer Institute for work on better biomarkers. But payers must do their part, too.

In this issue, we feature a review of the state of reimbursement for molecular testing in non–small cell lung cancer, including a selection of medical policies from different payer types around the country. With the FDA’s recent approval of Foundation Medicine’s first comprehensive diagnostic test for solid tumors, this will be an important area of reimbursement policy to watch.

As we search for solutions to giving cancer patients access to leading-edge treatments, FDA Commissioner Scott Gottlieb, MD, has won praise for working to make it easier for generics and biosimilars to reach the market. He’s been honest that, thus far, biosimilars in the United States have not been priced as high as some had hoped, in part because of the legal challenges competitors face. But biosimilars are starting to change the market in cancer care, as they take on some of the most established treatments on the market. In this issue, we hear from Hope Rugo, MD, who led the studies paving the way for approval for the trastuzumab biosimilar Ogivri, a competitor for the reference breast cancer drug Herceptin, which is expected to be available in 2019. Dr Rugo observes that not only do biosimilars create competition that helps patients and payers in the near term, but the savings they create gives payers resources for novel treatments reaching the market. To her, it’s a win-win.

Sincerely,

Mike Hennessy, Sr
Chairman and CEO

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Reimbursement Landscape for Molecular Testing in Non–Small Cell Lung Cancer (NSCLC)

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Future Shock: Embracing Disruption in the Immunotherapy Revolution

IN 1970, futurist Alvin Toffler published his book, Future Shock, which explored the idea that the pace of change was accelerating well past the ability of people to assimilate this change. The resulting sense of displacement and disorientation was reflected in the book’s title. We are now in a period of unprecedented rapid change in the domain of medical oncology. From emerging diagnostic technologies that leverage genomic, transcriptomic, and proteomic assessments of germline and somatic cell mutations to the analogous expanding portfolio of targeted and immuno-oncologic (IO) agents, the very nature of cancer care is changing at a pace that is difficult, at best, to assimilate. As the opportunities for more effective diagnosis and treatment grow at a near-exponential rate, our ability to deliver these therapeutics effectively and efficiently to patients in need is proving to be an increasingly formidable challenge.

The quantum leap in cancer care from the triad of surgery/radiation therapy/chemotherapy toward a new era of therapeutics enriched by IO agents has created both systemic and patient-specific challenges. In a recent paper in the *Annals of Oncology*, the authors note: “…An unprecedented number of new investigational agents and companies are entering the field of IO. As such, it has become challenging for oncology physicians conducting clinical trials, industry veterans developing IO drugs, and even regulators reviewing novel IO agents to keep track of the rapidly evolving landscape.”

These challenges also include the practical issues of how best to select patients for care using these agents, to the systems-based challenges of how best to deliver such highly complex care, at scale, in a financially sustainable way across the American healthcare system.

The proliferation of highly effective targeted therapies has markedly altered the nature of care and outcomes for patients with historically poor prognosis cancers, such as late-stage lung cancer, who may benefit from the use of targeted IO agents, such as the checkpoint inhibitors. For patients with non-small cell lung cancer (NSCLC), the 5-year overall survival for patients responsive to checkpoint inhibitors has quintupled over that of historic controls. The potential of these agents to markedly improve patient outcomes is just one example of the potential of IO and targeted therapeutics to produce better care outcomes. In this month’s edition of *Evidence-Based OncologySM* (*EBO*), we review the IO domain from perspectives ranging from that of the evolving standards of care for NSCLC to that of a patient who is undergoing IO treatment. Researchers from the Analysis Group review key changes in the evolving molecular/genomic diagnostic technologies that are helping to change the prognosis for patients with NSCLC. In an interview, Jeffrey S. Weber, MD, PhD, provides his perspective on IO. And in a remarkable series of interviews, Mary Caffrey brings forth the voices of patients who have navigated the complexities of clinical trials related to immunotherapy. Their courage and resilience in the face of their respective cancer journeys powerfully convey the human dimensions of our evolving cancer armamentarium.

As the technologies at the heart of this new era of cancer diagnosis and therapeutics continue to evolve at a rate that is near impossible to assimilate, the challenges to cope with this emerging future will force us to grapple with the effects of our “future shock.” In conversations, such as those fostered by *EBO™* amongst the respective cancer care stakeholders, we hope to help ground the future in sustainable systems that are dedicated to ensuring the increasing efficiency, effectiveness, and equitable distribution of this life-changing care technologies. ◆

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**EDITORIAL MISSION**

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.
With Approval of CAR T-Cell Therapy Comes the Next Challenge: Payer Coverage

Mary Caffrey

WHEN FDA APPROVED THE chimeric antigen receptor (CAR) T-cell therapy in August 2017, the news made headlines around the world: in this process, a patient's own genetically modified T-cells are engineered to express receptors that latch on to a specific cell surface protein, connecting them to cancer cells to be destroyed.1 Treatments for individual patients take weeks to create, to say nothing of the costs of care to receive the therapy or the millions to develop it.2

It all adds up to some of the most expensive therapies ever invented. The first CAR T-cell therapy, tisagenlecleucel (Kymriah)—a treatment for children and young adults with B-cell acute lymphoblastic leukemia (ALL) developed by Novartis—was priced at $475,000 for a one-time treatment.1 Axicabtagene ciloleucel (Yescarta), Kite Pharma/Gilead’s treatment for adult patients with relapsed or refractory large B-cell lymphoma, soon followed, priced at $373,000.4 Such ground-breaking therapies, with equally unprecedented prices, would clearly change the way payers did business.

Express Scripts’ chief medical officer Steve Miller, MD, did not hold back in a September blog post, saying the arrival of gene therapies would demand payment models “as novel as the medications themselves.”5 Critics of the cost of the Kymriah, writing in Evidence-Based Oncology™ (EBO™) went to press, said the issue of cost matters because CAR T-cell therapies are expected to receive FDA and overseas approval to treat many other blood cancers, including adult ALL, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma. They argue Novartis should be charging only $160,000 per treatment, in part because so many millions in federal research funds helped spark CAR T-cell discoveries.4

For now, there’s a lot of uncertainty, as both government and commercial insurers, and a handful of the nation’s leading cancer centers, navigate a reimbursement structure that truly has no precedent. “Ideas on the table include paying for a treatment over time, establishing insurer risk pools and financing one-time payments,” Miller wrote. “A successful model must address patients who change insurers or employers, and tracking their health outcomes over time to ensure payments aren’t being made if the treatment stops being effective.”6

Aaron Chrisman, director for Stem Cell Transplant and Cellular Therapy Administration at the University of Chicago Medicine, told EBO™ in an email that the approval and reimbursement process is necessarily painstaking because of the nature of the treatment, not just its high cost. “Because each product is designed for a specific patient, the cells, millions of them, must be produced for 1 patient at a time,” he said. “It can take 2 to 4 weeks to insert the new, molecularly engineered receptor and grow the required number of cells.”

As Chrisman explained, once the customized treatment is returned to the hospital and infused, the modified T-cells multiply and set out to find and attack the cancerous B-cells. Other reports have told of serious short-term side effects, including disorientation and tremors,7 so beyond the cost of therapy itself are the hospitalization costs.

For those on the front lines, connecting very sick cancer patients with a potentially life-saving treatment takes the involvement of the highest levels of leadership at an institution. At this stage, “there is a tremendous amount of oversight in each case,” from the cellular therapy program itself, to managed care, revenue cycle, supply chain, and pharmacy among others, Chrisman said in the email. “This will hopefully lessen over time, but currently it requires a substantial investment in time in order to obtain approvals and to ensure payment happens in a timely and accurate fashion.”

Medicare and Medicaid
CAR T-cell therapy’s groundbreaking nature—and the learning curve involved for all stakeholders—makes information on reimbursement hard to pin down. On the day of the FDA approval, Novartis announced an outcomes-based arrangement with CMS, to “eliminate inefficiencies from the healthcare...
PAYER COVERAGE
system, “with Kymriah as the first therapy subject to the agreement.” In short, CMS won’t pay for those patients who fail to respond in the first 28 days of treatment. A person familiar with CMS reimbursement policy told EBO™ the following about Medicare reimbursement for CAR T-cell therapy, as of January 19, 2018:

- CAR T-cell therapy treatment will only be reimbursed for hospitals or health systems for inpatient and outpatient settings
- Individual or small group practices will not be reimbursed. Those familiar with the treatment said this made sense due to the acute side effects that can occur.
- Inpatient cost for CAR-T will be bundled into the total cost of inpatient stay. If Medicare’s payment does not cover costs, CAR T-cell treatment may qualify under the acute inpatient “outlier” Prospective Payment System (PPS)
- As of January 1, 2018, Kymriah, which was the first CAR T treatment to be approved, has an outpatient code: ASP+6% for outpatient prospective payment ($503,500)
- As of January 1, 2018, Yescarta did not have an outpatient code; it could be allocated a “not otherwise classified” code

Novartis and Gilead report progress in obtaining commercial coverage; Gilead reported that commercial payers would likely account for between 50% and 60% of Vescarta’s users, and thus far most commercial payers were willing to cover the treatment. The University of Chicago Medicine’s Chrisman said thus far, commercial coverage for CAR T-cell therapy has occurred through individual contracts. “This can be a long process depending on the payer,” he said. “However, we will try our hardest for the sake of all our patients.” As of late January, 4-5 patients were awaiting confirmation of coverage and payment terms at the institution.

Novartis’ Althoff said patient access programs are also available. “Novartis is committed to ensuring eligible patients have access to Kymriah,” he wrote. “This includes co-pay assistance and travel assistance for transportation and accommodations for eligible patients and up to 2 caregivers to support compliance with the safety monitoring period.”

Does the Novartis model need to go a step further, of having billing codes ready when these expensive therapies are approved? “This would likely shorten the time to therapies being widely used, and would certainly help reduce uncertainty around reimbursement and coverage for providers,” Chrisman said. “This would need to go beyond just the creation of billing codes; therapies like CAR T-cell include the product itself as well as a variety of inpatient and outpatient services.” The best bet, he said, would be figuring out how to bill for everything before, or very soon after FDA approval occurs.

As more patients undergo treatment with chimeric antigen receptor T cells, we will learn to better manage cytokine release syndrome.

For Kymriah, state-level Medicaid policies matter due to its pediatric indication. Over 2 months, EBO™ contacted the press office at Penn Medicine, the center for Kymriah’s clinical trials, but received no response to questions about reimbursement. Spokespersons for the New Jersey and Pennsylvania Departments of Human Services, which oversee Medicaid programs closest to Penn, said Kymriah and Yescarta were both covered on an inpatient basis only; in Pennsylvania, Medicaid will only reimburse for FDA-approved indications, not investigational uses.

When contacted by EBO™, Eric Althoff, head of Global Media Relations, Novartis, referenced a Q-code approved for Medicare that became effective January 1, 2018, and said in an email “a number of state Medicaid programs have published Kymriah Medicaid policies,” but offered no specifics.

Commercial Coverage, Pharma Assistance
In emails to EBO™, spokespersons for both Novartis and Gilead referenced the creation of billing codes; therapies like CAR T-cell therapies include the product itself as well as a variety of inpatient and outpatient services.

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Long-Term Follow-Up of CAR T in ALL Suggests Early Treatment Extends Survival

A L O N G - T E R M F O L L O W - U P analyzing the toxic effects and results from a phase 1 clinical trial of adult patients with relapsed B-cell acute lymphoblastic leukemia (ALL) who were treated with CD19-specific chimeric antigen receptor (CAR) T cells found patients with low disease burden had a longer median overall survival (OS) and a lower incidence of toxicity. The study, published in New England Journal of Medicine, had 3 stages to evaluate safety and efficacy of 2 doses of CAR T cells and conditioning chemotherapy regimens. A total of 53 patients received 19-28z CAR T cells. The safety outcomes that the researchers focused on were incidence of cytokine release syndrome (CRS) and neurotoxic events. They also studied complete remission (CR) rate and OS and EFS.

“We hypothesized that the safety and long-term efficacy of 19-28z CAR T cells may be associated with clinical characteristics of the patients, disease characteristics, the treatment regimen, and the kinetics of T-cell expansion,” the authors wrote.

They found that CRS occurred in 26% of the patients, including 1 patient who died, and the rate of severe neurotoxicity was 42%. There was CR in 83% of patients. The median OS was 12.9 months and the median EFS was 6.1 months. The median follow-up time was 29 months.

The results, which represent the longest follow-up of people with ALL treated with CAR T therapy, “confirms the power of CAR T cells,” said Jae Park, MD, a medical oncologist at Memorial Sloan Kettering (MSK) Cancer Center and the principal investigator of the phase 1 trial.

“With the long follow-up, we were able to demonstrate for the first time that patients with a lower disease burden benefited the most from CAR therapy, with significantly improved survival and reduced toxicity,” he said.

The OS was 12.9 months, but patients with a low disease burden had a median OS of 20.1 months.

REFERENCE
Reimbursement Landscape for Molecular Testing in Non–Small-Cell Lung Cancer (NSCLC)

Dave Nellesen, PhD; Katerine Dea, MSc; Annie Guerin, MSc; Kenneth W. Culver, MD; Alex Mutebi, PhD; and Anand Dalal, MBA, BPharm

MOLECULAR TESTING

Précis: This review assesses the current molecular testing landscape for non–small-cell lung cancer in the United States.

ABSTRACT

Introduction: The identification of oncogenic genomic alterations and the development of matched targeted therapies have made molecular testing an increasingly important approach to treat non–small cell lung cancer (NSCLC). However, little information is available concerning use of molecular testing in clinical practice and about coverage of these novel tests.

Areas covered: In particular, clinical guidelines and consensus recommendations, currently available molecular tests along with their associated advantages and disadvantages, the use of molecular testing in clinical practice, and current managed care coverage policies.

Commentary: The landscape for molecular testing in NSCLC is evolving rapidly. Although targeted therapy in patients with specific oncogenic genomic alterations is associated with superior outcomes, the use of molecular testing in clinical practice is hindered by several factors, including long turnaround times and tissue sample requirements. Clinical guidelines support the use of broad molecular testing in NSCLC, but most US health plans cover testing only for a limited number of genomic alterations. Nevertheless, as testing technology improves and targeted therapies become more available, molecular tests are expected to eventually become the standard of care in NSCLC treatment.

KEY TO GENE NAMES

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALK</td>
<td>ALK receptor tyrosine kinase</td>
</tr>
<tr>
<td>BRAF</td>
<td>B-Raf proto-oncogene, serine/threonine kinase</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>HER2</td>
<td>erb-b2 receptor tyrosine kinase 2</td>
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<tr>
<td>KRAS</td>
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<tr>
<td>MET</td>
<td>MET proto-oncogene, receptor tyrosine kinase</td>
</tr>
<tr>
<td>RET</td>
<td>ret proto-oncogene</td>
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<tr>
<td>ROS1</td>
<td>ROS proto-oncogene-1, receptor tyrosine kinase</td>
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Source: Hugo Gene Nomenclature Committee.

NSCLC have recently been updated to include BRAF mutation testing in the standard set of biomarkers that should be assessed for patients with NSCLC, with the recommendation to use dabrafenib plus trametinib in first-line therapy for BRAF V600E–mutant metastatic NSCLC. The identification of novel driver mutations defining clinically relevant molecular subtypes of NSCLC has made molecular testing and subtyping an increasingly important diagnostic tool. Molecular testing using next-generation sequencing (NGS) technology has emerged as a tissue- and time-efficient testing approach as it allows an entire panel of genotypes to be tested simultaneously, typically requiring a small tissue sample. Accordingly, several clinical guidelines now endorse the use of broad molecular testing to identify actionable driver mutations for which targeted agents may be available.

In light of the accumulating evidence for the value of molecular testing in NSCLC, it is important to understand current patterns in molecular testing in lung cancer in US clinical practice, particularly the use of multiplex testing by NGS. Testing in actual clinical practice may be particularly important in NSCLC, it is important to understand current patterns in molecular testing in lung cancer in US clinical practice, particularly the use of multiplex testing by NGS. Testing in actual clinical practice may be particularly important in NSCLC, and for patients with relatively rare genomic alterations, given the increasing number of available targeted therapies. Considering the need to identify the appropriate targeted therapy for the right NSCLC patients, and the risk of running out of tissue in sequential testing modalities, multiplex testing may be even more important in NSCLC because of its many less-common actionable driver mutations/alterations, such as BRAF mutations. Anecdotally, patient access to molecular testing for both established and emerging NSCLC driver mutations also varies, with medical coverage policies that may not reflect current scientific and medical consensus in this rapidly changing area.
MOLECULAR TESTING

To address this knowledge gap and better understand the current molecular testing landscape for NSCLC in the United States, this targeted literature review included the following 4 objectives:

1. Describe published clinical guidelines and consensus recommendations related to the use of molecular testing in patients with NSCLC.
2. Describe molecular diagnostic tests currently available in the United States for the detection of the BRAF mutations, their use in clinical practice, and their associated advantages and disadvantages from the point of view of both patients and physicians.
3. Describe current managed care policies regarding the coverage of molecular testing for NSCLC.
4. Identify policies and barriers regarding the use of molecular testing in clinical practice, and the implications and ramifications they present to the molecular testing landscape for NSCLC.

Methods

Data Sources

To identify relevant information regarding the 4 study objectives listed above, a targeted literature review was conducted using the following data sources: 1) MEDLINE and EMBASE (via Ovid); 2) published abstracts from the American Society of Clinical Oncology (ASCO); 3) published treatment and diagnostic oncology guidelines from ASCO, the NCCN, and the College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP); 4) published or otherwise publicly available care pathways including diagnostic testing for NSCLC; 5) medical policies describing coverage for molecular diagnostic tests for NSCLC tumor samples that include BRAF mutations; 6) grey literature, including pharmaceutical, molecular diagnostic and managed care industry websites, white papers, trade press, and newsletters (eg, PinkSheet, GreySheet, GenomeWeb, Oncology Times, Evidence-Based Oncology™, Managed Care magazine), describing relevant molecular tests and their coverage and reimbursement; and 7) ad hoc Internet and PubMed searches.

Search Strategy

Peer-reviewed articles

Peer-reviewed articles identified during the targeted literature review were selected based on their potential relevance to the 4 study objectives. The search focused on articles published between January 1, 2011, and June 6, 2016, and was limited to English articles focusing on the United States.

The search strings used to conduct the target literature review in Ovid MEDLINE and EMBASE contained the terms BRAF, B-Raf, or B Raf and 1 carcinoma, non–small-cell lung/ or non–small-cell lung cancer$ or squamous cell cancer$ or adenocarcinoma, bronchogenic/ or adenocarcinoma, bronchioalveolar/ or carcinoma, large cell/ or carcinoma, squamous cell/ or lung or NSCLC or non–small-cell lung cancer.

Clinical guidelines

The 3 main US oncology guidelines for the diagnosis and treatment of NSCLC were selected a priori: ASCO, NCCN, and CAP/IASLC/AMP guidelines. Searches for current guidelines were conducted initially in June 2016 and updated in November 2017.

Molecular diagnostic tests

Molecular diagnostic tests that detect the BRAF V600E mutation and other genomic alterations using NGS were selected based on internet searching. To be eligible for inclusion, the tests were required to be marketed for diagnostic use in lung cancer, commercially available in the United States, and used or produced by large central/national laboratories, molecular diagnostics specialty companies, or academic laboratories. It should be noted that, because of the nonsystematic nature of the search, the tests that were selected for this study are not necessarily representative and/or inclusive of all the tests that are currently available on the US market.

Payer medical policies

Payer medical policies (ie, coverage policies) were identified by searching the websites of small and large US healthcare plans. Searches for publicly available medical policies were conducted initially in June and July of 2016.

Results and Discussion

A total of 73 articles relevant to the study objectives were identified and selected: 1 was related to objective 1,14 to objective 2,11 to objective 3,2,25,30,31,33,34,35,36,37,38,39 and 11 to objective 4.2,26,31,33,34,35,36,37,38,39,40,41,42,43 A total of 19 currently available molecular tests for the detection of the BRAF V600E mutation were selected and reviewed: 3 were from large central/national laboratories, 14 from molecular diagnostics specialty companies, and 2 from academic laboratories. A total of 16 healthcare plans were selected and their medical policies regarding the coverage of molecular tests for patients with NSCLC were reviewed. The results obtained by reviewing the above selections are presented below for each of the 4 study objectives.

Available Molecular Tests for the BRAF V600E Mutation: Practical Advantages and Disadvantages

Available molecular tests

A description of the characteristics of a selection of currently available molecular tests for the detection of the BRAF V600E mutation in patients with NSCLC.

Table 1. Guideline Recommendations for Molecular Testing of NSCLC

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Summary of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN (2018)</td>
<td>The NCCN panel strongly endorses broader molecular profiling (also known as precision medicine) to identify rare driver mutations to ensure that patients receive the most appropriate treatment.</td>
</tr>
<tr>
<td>CAP/IASLC/AMP (2016)</td>
<td>Molecular Testing Guideline for Selection of Lung Cancer Patients (Draft recommendations, June 28, 2016). Multiplexed genetic sequencing panels are recommended to identify BRAF, MET, KRAS, HER2, and RET mutations either initially or when routine EGFR, ALK, and ROS1 testing are negative. Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1.</td>
</tr>
<tr>
<td>ASCO (2014)</td>
<td>The ASCO review panel endorses the 2013 CAP/IASLC/AMP guidelines. The CAP/IASLC/AMP guideline recommends prioritizing EGFR and ALK testing over other biomarkers, but it is noted that new important testing indications, notably ROS1 and RET rearrangements, emerged while the guideline was under development.</td>
</tr>
</tbody>
</table>

NCCN indicates National Comprehensive Cancer Network; NSCLC, non–small cell lung cancer.

More specifically, they recommend molecular testing be performed to identify genomic alterations in BRAF, MET, KRAS, HER2, and RET, either initially or when routine EGFR, ALK, and ROS1 tests are negative.11,12 It should be noted that the CAP/IASLC/AMP guidelines were first published online in 2013. Revised 2016 draft recommendations were anticipated for publication in early 2016, however, as of November 2017 updated guidelines have not been published.

NCCN guidelines continue to support broad molecular profiling (Table 1), and they recommend testing for ALK gene rearrangements and EGFR mutations (category 1 for both) in the NSCLC algorithm for patients with nonsquamous NSCLC or NSCLC not otherwise specified so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as ceritinib, erlotinib, gefitinib, afatinib, and crizotinib. The NCCN guidelines also recommend testing for ROS1 rearrangements (category 2A) as well as for BRAF V600E mutations for patients with metastatic NSCLC. These guidelines also state that other driver mutations and gene rearrangements (ie, driver events) are being identified, such as RET gene rearrangements, high-level MET amplification or MET exon 14 skipping mutation, and HER2 (also known as ERBB2). Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications.13-15 ASCO guidelines date back to 2014, when the ASCO staff reviewed and endorsed the 2013 CAP/IASLC/AMP guidelines (Table 1). At that time, the CAP/IASLC/AMP guidelines only addressed the use of molecular testing for the selection of patients with lung cancer with genomic alterations in EGFR and ALK.16,17

There are a variety of NSCLC care pathways. Anthem Cancer Care Quality Program Treatment Pathways do not specify which protocols should be used for molecular testing. Overall, care pathways were not publicly available and mostly focused on chemotherapy, targeted therapy, and supportive care regimens.18,19

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Available Molecular Tests for the BRAF V600E Mutation: Practical Advantages and Disadvantages

Available molecular tests

A description of the characteristics of a selection of currently available molecular tests for the detection of the BRAF V600E mutation in patients with NSCLC.
is presented in Table 2. BRAF tests are available both as single analyte tests and as part of multigene panels. Besides BRAF, a growing number of lung cancer panels also assess genomic alterations in several other genes, including ALK, EGFR, HER2, KRAS, MET, RET, and ROS1. To identify BRAF mutations, various test technologies are used, with detectable classes of genomic alterations varying with the tests.

As illustrated in Table 2, some tests detect only point mutations while others are more comprehensive and detect genomic alterations such as insertion and deletions (indels), chromosomal rearrangements, and copy number alterations. One implication of this variability across tests is that not all the actionable—and thus treatable—driver mutations in NSCLC are identified by all available tests. Not surprisingly, the cost of comprehensive panel testing appears to be substantially higher than the cost of single nucleotide polymorphism tests.

Sample requirements for available tests vary, as summarized in Table 3. While most tests require formalin-fixed paraffin-embedded tissue, some also accept a blood/liquid biopsy sample, or purified DNA. Several tests have been developed/validated

---

### Table 2. A Selection of Tests Currently Available to Detect BRAF V600E in NSCLC Patients—Test Description

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples of Test Names</th>
<th>Provider/Organization</th>
<th>Covered Genes of Interest*</th>
<th>Detection of Classes of Genomic Alterations*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large central/national laboratories</td>
<td>Lung Cancer Comprehensive Mutation and Translocation Panel by NGS</td>
<td>ARUP Laboratories</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>OncoVantage</td>
<td>Quest Diagnostics</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, and RET</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>IntelliGEN</td>
<td>LabCorp</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, and RET</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>FoundationOne</td>
<td>Foundation Medicine</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1*</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Guardant 360</td>
<td>Guardant Health</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>OncoGXLung</td>
<td>Rosetta Genomics</td>
<td>BRAF, ALK, EGFR, KRAS, and ROS1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>PCR - RosettaGX</td>
<td>Rosetta Genomics</td>
<td>BRAF, EGFR, and KRAS</td>
<td>✓</td>
</tr>
<tr>
<td>Molecular diagnostics specialty companies</td>
<td>Lung Cancer NGS Panel - M LUNG NGS</td>
<td>Molecular Pathology Laboratory Network, Inc</td>
<td>BRAF, ALK, EGFR, and KRAS</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>GeneTrails NSCLC Genotyping Panel</td>
<td>Knight Diagnostic Laboratories</td>
<td>BRAF, EGFR, HER2, and KRAS</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>OncoPlexDx - Protein Expression Panel and Gene Mutation Panel</td>
<td>NantOomics</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, and RET</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Mi Profile X</td>
<td>Caris Molecular Intelligence</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>OnkoMatch</td>
<td>GenPath</td>
<td>BRAF, EGFR, and KRAS</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>SmartGenomics</td>
<td>PathGroup</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The Paradigm Center Diagnostic (PcDx) Panel</td>
<td>Paradigm</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Academic laboratories</td>
<td>UW-OncoPlex - Cancer Gene Panel</td>
<td>University of Washington - Laboratory Medicine</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)</td>
<td>Memorial Sloan Kettering (MSK) Cancer Center</td>
<td>BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1</td>
<td>✓</td>
</tr>
</tbody>
</table>

CNA indicates copy number alteration; NGS, next generation sequencing; SNP, single nucleotide polymorphism; US, United States.

*Includes only tests available in the United States. Only genes explicitly specified on websites are reported. More genes may be covered by the tests.

†Types of genomic alterations were not identified based on genes detected by the tests. Ability to detect copy number alteration, copy number variation, or DNA amplifications. Additional genes included in assay: a current list is available at foundationsmedicine.com/genomic-testing/

| Foundations one MSK-IMPACT authorized to identify mutations in 408 genes, refer to MSK website for further details: msk-impact.org/impact.

* The classes of genomic alterations identified with an * are not specifically stated. They are inferred based on the covered genes that are mentioned on the websites. Information provided in the websites was limited.
specifically for lung cancer, while other tests may be applied to any solid tumor or are specific to hematologic malignancies.

Test turnaround time from sample collection to availability of results varies widely across tests, ranging from 1 to 4 days to 6 weeks (Table 4). Test performance also varies and, in addition, is not reported consistently. Similarly, the information available for each test was often incomplete and not reported consistently. For instance, the sensitivity, specificity, and sequencing depth and coverage of the tests were rarely provided.

Very little was found regarding testing patterns in clinical practice. In particular, no information directly related to the clinical practice of *BRAF* testing was found. The information available was related only to *EGFR* and did not encompass all types of genomic alterations. Anecdotally evidence suggests a rapid increase in the availability of comprehensive genomic profiling tests and their use by physicians in treatment selection. As a case in point, Foundation Medicine conducted more than 8000 FoundationOne and FoundationHeme NGS tests in the third quarter of 2015, a 25% increase from the previous year. In addition, a global survey conducted by Kantar Health between December 2014 and January 2015 found that overall 81% of newly diagnosed patients with stage IIb/IV NSCLC received testing for *EGFR* prior to first-line therapy; this percentage was lower among patients treated by US and European oncologists (77%).

**Practical advantages and disadvantages**

Comprehensive genomic profiling tests that assay and detect various types of driver mutations have substantial advantages for patients and physicians (Table 2). As long as the information provided by these tests is actionable—and thus has clinical utility—clinical outcomes are likely to improve. Several studies have investigated the utility of molecular testing in patients with NSCLC by comparing different tests and methodologies. In 1 of these studies, evidence for the utility of targeted NGS assays was obtained by comparing the information obtained from a single gene assay and NGS assays. The study showed that 50-gene panel assays were able to identify at least 1 actionable gene variant in almost twice as many specimens than single gene assays. However, the practical implications of the potentially useful clinical information provided by molecular testing remain unclear, as no studies quantifying the benefit of improved test performance for patients and/or payers were identified. However, time to results for all actionable genomic alterations and technical improvements related to diminished sample requirements with a 50-gene panel may have substantial advantages for both patients and physicians (Table 3). Newer tests are becoming more efficient in detecting NSCLC genomic variants and they require gradually smaller amounts of sample tissue. This is particularly important given that the limited amount of tissue typically available from a lung biopsy needs to be used in multiple histological and pathological tests, including resampling, following a diagnosis of NSCLC.

Importantly, tests can now be performed using samples that require less invasive procedures, such as a liquid biopsy. Several articles assessed the use of these less invasive procedures.

Although liquid biopsy has been validated for *EGFR* testing, its reliability for NSCLC panel tests compared with direct analysis of tumor tissue has not been established.

A fast test turnaround time may be critical to inform clinical decision making (Table 4). Reported turnaround times varied widely. No studies assessing real-world turnaround times or the impact of MOLECULAR TESTING

**TABLE 3. A Selection of Tests Currently Available to Detect *BRAF* V600E in Patients With NSCLC—Sample Requirements**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples of Test Names</th>
<th>FFPE Block or Tissue</th>
<th>Fine Needle Biopsy</th>
<th>Blood/Liquid Biopsy Sample</th>
<th>Purified DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large central/ national laboratories</td>
<td>Lung Cancer Comprehensive Mutation and Translocation Panel by NGS</td>
<td>Resections: 8 unstained 5-micron slides (&gt;5 slides) Small biopsies: 15 unstained 5-micron slides (&gt;10 slides)</td>
<td>Yes</td>
<td>2 ml whole blood</td>
<td>10 ul extracted DNA</td>
</tr>
<tr>
<td></td>
<td>IntelliGEN</td>
<td>Five unstained slides and one matching H&amp;E stained slide cut at 10 μM</td>
<td></td>
<td>5 ml to 10 ml fine needle aspirate</td>
<td>✗</td>
</tr>
<tr>
<td></td>
<td>FoundationOne</td>
<td>≥40 μm tissue, of which a minimum of 20% is of malignant origin, on 8 to 10 unstained slides or in an FFPE block</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guardant 360</td>
<td>Lung Molecular Profiling 2 FFPE block containing non-necrotic tumor tissue, plus 1 H&amp;E slide cut at 4.5 microns or biopsy or 12 unstained slides at 10 μm thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OncoGXLung</td>
<td>GeneStrat OncoDEEP Lung Cancer NGS Panel - M LUNG NGS Gene Mutation Panel Genotyping Panel</td>
<td>3.5 slides at 5 microns minimum</td>
<td>20 ng DNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OncoPlexDx - Protein Expression Panel and Gene Mutation Panel</td>
<td>One 5 μm H&amp;E section and 2-3 10 μm sections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI Profile X OnkoMatch</td>
<td>The Paradigm Center Diagnostic (PCDX) Panel Six to ten 10 μm thick freshly cut curls along with H&amp;E stained section of same block - 75 mm3 (5 mm x 5 mm x 3 mm)</td>
<td>4 to 6 needle biopsies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UW-OncoPlex - Cancer Gene Panel</td>
<td>U8-OncoPlex - Cancer Gene Panel</td>
<td>1 slide at 4-micron thickness stained with H&amp;E and 10 unstained, non-baked slides at 10-micron thickness (≥5 unstained slides)</td>
<td>1 to 2 ml</td>
<td>6 ml blood</td>
</tr>
<tr>
<td></td>
<td>MSK-IMPACT</td>
<td>(Integrated Mutation Profiling of Actionable Cancer Targets)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FFPE indicates formalin-fixed paraffin-embedded; H&E, hematoxylin-and-eosin; MSK: Memorial Sloan Kettering Cancer Center; NSCLC: non–small cell lung cancer; US: United States.

*Includes only tests available in the US.

**Update**

As of December 2017, other approved NGS tests included Oncomine Dx as well as the broader FoundationOne CDx (FICDx) and Memorial Sloan Kettering Cancer Center’s Integrated Mutation Profiling of Actionable Cancer Targets.
MOLECULAR TESTING

Profilin of Actionable Cancer Targets (MSK-IMPACT), which are both approved to detect mutations in more than 300 genes in any solid tumor type, including NSCLC, melanoma, and breast cancer, enabling the identification of patients who may benefit from at least 15 different FDA-approved targeted therapies.

US Managed Care Policies

In terms of coverage, managed care policies regarding molecular testing in NSCLC vary considerably (Table 5). Most of the medical policies identified in this review cover only ALK and EGFR testing. For example, a number of Blue Cross Blue Shield medical policies are similar and usually consider only ALK and EGFR testing as medically necessary. A few plans, such as Health Net, Inc. and CMS, cover testing for genomic alterations in BRAF, ALK, EGFR, HER2, KRAS, MET, RET, and ROS1. NCCN guidelines are typically cited in medical policies as the reason some tests are deemed medically necessary and others are not. Although most plans align medical policies with anatomical tumor location, some payers such as Health Net, Inc., UnitedHealthcare, Aetna, and several CMS Local Coverage/Medicare contractors have issued medical policies covering comprehensive genomic profiling of tumors using NGS. Standard guidelines for coverage of molecular diagnostic tests have been proposed by the Center for Medical Technology Policy, but they have not generally been put into practice. Similarly, in 2011, the Molecular Diagnostic Services (MolDX) Program was created to establish clear expectations for coverage and reimbursement of molecular diagnostic tests. Based on this review of managed care policies for diagnostic tests, adherence to MolDX recommendations on the part of diagnostic developers and application of these guidelines by payers is not apparent.

Current Molecular Testing

Landscape in NSCLC

The technology to detect genomic alterations continues to improve, and several studies have shown that NGS-based assays are capable of more precisely detecting a wider range of alterations than are standard non-NGS tests. These findings underscore not only the greater efficiency of NGS testing in the detection of genomic alterations, but also the importance in identifying the right patients who could benefit from targeted therapies.

Nevertheless, there is currently a wide variation in clinical practice for molecular testing in NSCLC. A variety of tests with different characteristics, sample requirements, and reimbursement levels are available on the market, making it challenging for physicians to select the most appropriate test for their patients. In addition, the complexity of genomic information provided by the tests creates substantial challenges in interpreting the results of a test. The growing number of identified genetic variants and the increasing technical complexity of molecular tests are likely to exacerbate this problem.

While great strides have been made in advancing molecular diagnostics, several hurdles still need to be overcome to make molecular testing a routine tool for diagnostic workup of patients with NSCLC. In a global survey conducted, the main reasons (aside histology and general patient health) reported by oncologists for not testing for genomic alterations in EGFR included insufficient tumor tissue and long turnaround time. More specifically, because of the long turnaround time, 26% of US physicians made their treatment decisions before test results were made available. Sequential single gene testing can leave an insufficient amount of tissue to analyze additional genomic alterations, an issue seen by oncologists as an important barrier to testing.

To address the issue of limited tissue availability, CAP/IASLC/AMP guidelines recommend liquid biopsy/circulating tumor DNA (ctDNA) assay be used for EGFR testing when tissue is insufficient for molecular testing. These guidelines also state, “Pathologists and laboratories should utilize tissue-sparing techniques to preserve tumor tissue for diagnosis and to enable subsequent lung cancer biomarker testing.” In addition, NCCN guidelines recommend broad molecular testing. Regarding ctDNA, the NCCN guidelines state, “Recent data suggest that plasma genotyping (also known as liquid biopsy or plasma biopsy) may be considered instead of tissue biopsy to detect whether patients have T790M; however, if the plasma biopsy is negative, then tissue biopsy is recommended, if

### Table 4: A Selection of Tests Currently Available to Detect BRAF V600E in Patients With NSCLC – Test Performance

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples of Test Names</th>
<th>Depth/ Coverage</th>
<th>Lung Specific</th>
<th>Solid Tumor Specific</th>
<th>Turnaround Time</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Allele Burden Cut-Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large central/national laboratories</td>
<td>Lung Cancer Comprehensive Mutation and Translation Panel by NGS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>12-14 days</td>
<td>✓</td>
<td>✓</td>
<td>5% mutant alleles</td>
</tr>
<tr>
<td></td>
<td>OncoVantage ^1^</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>14 days</td>
<td>✓</td>
<td>✓</td>
<td>5% mutation</td>
</tr>
<tr>
<td></td>
<td>IntelISEN ^2^</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>14-21 days</td>
<td>✓</td>
<td>✓</td>
<td>Detect mutation present at 5% of background wild-type DNA</td>
</tr>
<tr>
<td>Molecular diagnostics specialty companies</td>
<td>FoundationOne</td>
<td>&gt;500x</td>
<td>✓</td>
<td>✓</td>
<td>14 days</td>
<td>✓</td>
<td>✓</td>
<td>&gt;90% (in rearrangements to &gt;99% (base substitutions))</td>
</tr>
<tr>
<td></td>
<td>Guardant 360</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>14 days</td>
<td>✓</td>
<td>✓</td>
<td>99.9999%</td>
</tr>
<tr>
<td></td>
<td>OncoGXlung</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>7-10 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR - RosettaGX</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1-4 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung Molecular Profile</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>12 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GeneStrat</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>3 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OncoDEEP</td>
<td>1000x</td>
<td>✓</td>
<td>✓</td>
<td>7 days</td>
<td>✓</td>
<td>✓</td>
<td>&gt;99% (mdx)</td>
</tr>
<tr>
<td></td>
<td>Lung Cancer NGS Panel - M-LUNG NGS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>7-10 days</td>
<td>✓</td>
<td>✓</td>
<td>≤10% mutant allele</td>
</tr>
<tr>
<td></td>
<td>GeneTrails NSCLC Genotyping Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>10-14 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OncoPlexDx Protein Expression Panel and Gene Mutation Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mi Profile X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OnkoMatch</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SmartGenomics 1000x avg</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>7-10 days</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The Paradigm Center Diagnostic (PcDx) Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>4-5 days</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>5000x depth of coverage</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>4-6 weeks</td>
<td>✓</td>
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<td></td>
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<tr>
<td></td>
<td>UW-OncoPlex - Cancer Gene Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NGS indicates next generation sequencing; MSK, Memorial Sloan Kettering Cancer Center; NSCLC, non–small cell lung cancer; US, United States

*Includes only tests available in the US

4_EBO_Molecular_Testing-V3.indd
feasible.21 This tissue-sparing approach is being used by physicians across different tumor subtypes, substantially increasing the number of tests that can be conducted for each patient. Although some form of molecular testing is covered by most health plans, uncertain reimbursement may limit its use in clinical practice. According to test manufacturers, payment for covered molecular diagnostic tests is inconsistent and does not reflect the value of the information provided. For instance, some Clinical Laboratory Improvement Amendments laboratories describe low payment levels and limited coverage for molecular diagnostic tests, especially panel tests.21

In addition, private health plans may not reimburse tests that are not priced by Medicare and, in some instances, match Medicare prices that are below the actual costs of performing the test. For broad molecular profiling tests that include hundreds of genes, individual contracts between health plans and test manufacturers may overcome these limitations. As a case in point, UnitedHealthcare and Foundation Medicine recently reached an agreement according to which UnitedHealthcare will cover the FoundationOne test for patients with metastatic stage IV NSCLC.108

Consortia of test manufacturers may also help establish the value of comprehensive genomic profiling. In 2015, Thermo-Fisher, Illumina, Eli Lilly, Celgene, and Roche/Genentech committed to provide their competence and funds to Molecular Evidence Development Consortium—a nonprofit organization that aims to establish standards for molecular tests and build the clinical utility evidence around targeted treatment strategies.109 Moreover, statutory changes to Medicare may contribute to supporting value-based pricing for diagnostic tests. To this end, the implementation of a law that seeks to establish a market-based payment system for molecular tests—the Protecting Access to Medicare Act of 2014—is ongoing.

Medical policies establishing coverage for molecular testing face a tremendous challenge in keeping pace with technological advancement in molecular diagnostics. According to NextGen DX’s market analysis, more than 60,000 unique molecular diagnostic testing products are presently on the market and 8 to 10 new tests are estimated to be launched daily.110 The large—and increasing—number of available tests makes setting health plan coverage policies especially challenging, particularly given that the evidence supporting the clinical value of all genes in a comprehensive genomic profile is limited. Additionally, the medical policies of most health plans are updated far less frequently than the NCCN guidelines, and thus they are unlikely to keep up to date with the latest guideline recommendations. This is possibly the reason why some tests are not classified as medically necessary despite being listed in the most recent NCCN guidelines.

Establishing consistent coverage may depend on clear demonstrations of the value of molecular testing. One recent study compared the values of multiplex and sequential testing and concluded that sequential testing “is very inefficient especially with respect to the time it takes to complete testing,…[to] the total cost, and,…to the amount of tissue necessary to complete testing.”111 This targeted literature review did not identify any studies quantifying the benefits of multiplex testing or evaluating the clinical and economic outcomes associated with BRAF testing in NSCLC, either alone or in the context of a multiplex/panel test. More studies measuring the economic value of molecular testing and comparing different types of tests are needed for each genomic alteration. With such a vast number of existing testing options, information on the comparative effectiveness and cost-effectiveness of available tests will be crucial to help physicians select the most clinically appropriate test and assist health plans in making more informed coverage and reimbursement decisions.

CONCLUSIONS

The landscape for molecular testing in NSCLC is evolving rapidly, mostly due to significant technological advances that capture actionable information about disease subtypes with increasingly accurate results. Although treating patients with NSCLC who have driver mutations with appropriate targeted therapy is associated with superior outcomes, the use of molecular testing in clinical practice appears to be limited. The use of molecular testing may be hindered by several factors, including long turnaround times to generate test results and limitations on the availability of tumor tissue. In addition, although several clinical guidelines support the use of broad molecular testing in patients with NSCLC, most health plans only cover tests to identify genomic alterations in ALK and EGFR. Based on the information identified in our search of medical policies, only a few health plans extend their coverage to other genomic alterations in targets such as BRAF, HER2, KRAS, MET, RET, and ROS1.

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E-MAIL: Dave.Nellesen@analysisgroup.com

TABLE 5. A Selection of Medical Policies

<table>
<thead>
<tr>
<th>Examples of Test Names</th>
<th>Approximate Number of Covered Lives</th>
<th>Panel Testing</th>
<th>BRAF</th>
<th>ALK</th>
<th>EGFR</th>
<th>HER2 (ERBB2)</th>
<th>KRAS</th>
<th>MET</th>
<th>RET</th>
<th>ROS1</th>
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<td>Anthem-BlueCross</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>BlueShield</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>United Healthcare</td>
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<td>Excelus</td>
<td>1.5 million</td>
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<td>✓</td>
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<td>Universa</td>
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<td>Blue Cross Shield of Massachusetts</td>
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<td>✓</td>
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<tr>
<td>CMS Local Coverage Determinations</td>
<td>2 million</td>
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<td>✓</td>
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</tbody>
</table>

CIGP indicates comprehensive genomic profiling; LCD, local coverage determination; NSCLC, non-small cell lung cancer
*There is some contradictory information in the Astro policy. The BRAF V600 mutation analysis is reported as experimental and investigational for NSCLC. In contrast, according to the FDA’s FDA drug application, the test is reported as medically necessary because it is “reasonable and necessary to evaluate the presence of cancer.” Considered as medically necessary only in patients with advanced lung adenocarcinomas or in whom an adenocarcinoma component cannot be excluded. Analysis for EGFR mutations within exons 18-24 is considered investigational. “EGFR is covered only when the following conditions are met: a) Patient has been diagnosed with advanced stage IIIB or IV (N2 or M1) NSCLC; and, b) Patient is a lifetime nonsmoker or former light smoker with more than 10 cigarettes per day. c) Patient is female. d) Patient has not received prior systemic chemotherapy or radiation therapy. e) Patient has not received prior tyrosine kinase inhibitor therapy. f) Patient has not received prior anti-EGFR monoclonal antibody therapy. g) Patient has received prior at least systemic treatment. h) Patient has received prior surgery. i) Patient is undergoing or is scheduled to undergo surgery.”
FDA Grants Approval to Pertuzumab for Adjuvant Treatment in Patients with HER2-Positive Breast Cancer

Jaime Rosenberg

THE FDA HAS GRANTED APPROVAL to pertuzumab (Perjeta) to be used in combination with trastuzumab (Herceptin) and chemotherapy as adjuvant therapy for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer with a high risk of recurrence.1

In 2013, the FDA granted accelerated approval to pertuzumab as neoadjuvant treatment. This latest adjuvant approval fulfills the accelerated approval postmarketing process, and regular approval is now granted for pertuzumab as part of treatment for patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node-positive).

The full approval of Roche subsidiary Genentech’s pertuzumab comes after publication of data from theAPHINITY (NCT01358877) trial. The multicenter, randomized double-blind, placebo-controlled trial included 4804 patients with HER2-positive early breast cancer who had their primary tumor removed prior to randomization. Following tumor removal, the patients were randomized to receive either pertuzumab or placebo in combination with adjuvant trastuzumab and chemotherapy.2

The initial pertuzumab dose is 840 mg administered as a 60-minute intravenous infusion, followed by 420 mg administered as a 30- to 60-minute intravenous infusion every 3 weeks.

The authors assessed for invasive disease-free survival (IDFS), which was defined as the time from randomization to first occurrence of ipsilateral local or regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, or death from any cause. After a median follow-up of 45.4 months, the proportion of IDFS events in the intent-to-treat population was 7.1% (n = 171) in the pertuzumab arm and 8.7% for those administered placebo (hazard ratio [HR], 0.82; 95% CI, 0.67-1.00; P = .047). Patients with hormone receptor-negative or node-positive breast cancer were considered high-risk patients.

The proportion of IDFS events in patients with hormone receptor-negative disease was 8.2% (n = 71) in the pertuzumab arm and 10.6% (n = 91) in the placebo arm (HR, 0.76; 95% CI, 0.56-1.04). The proportion of IDFS events for patients with node-negative disease was 9.2% (n = 139) and 12.1% (n = 181) in the pertuzumab and placebo arms, respectively (HR, 0.77; 95% CI, 0.62-0.96). Adverse reactions reported in at least 30% of patients who received pertuzumab included diarrhea, nausea, alopecia, and fatigue. The most common grade 3 or 4 adverse reactions included neutropenia, febrile neutropenia, and leukopenia.

“The goal of treating breast cancer early is to provide people with the best chance for a cure. While we come closer to this goal with each advance, many people still have a recurrence and progress to the metastatic stage,” said Sandra Horning, MD, Roche’s chief medical officer and head of global product development, in a statement. “[The ] approval of Perjeta means people with HER2-positive early breast cancer at high risk of recurrence have a new, clinically meaningful treatment option to reduce the chances of their disease returning.”

In 2012, the FDA granted regular approval to pertuzumab for its use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who had not received prior anti-HER2 therapy or chemotherapy for metastatic disease.3

REFERENCES


IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood. IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 13 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 13%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Atrial Fibrillation: Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA®, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension (range, 6 to 17%) has occurred in patients treated with IMBRUVICA® with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting IMBRUVICA®. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Second Primary Malignancies: Other malignancies (range, 3 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with IMBRUVICA®. The most frequent second primary malignancy was non-melanoma skin cancer (range, 2 to 13%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA® therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions.

Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation.
of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise men to avoid fathering a child during the same time period.

**ADVERSE REACTIONS**

* **B-cell malignancies**: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (62%), neutropenia (61%), diarrhea (43%), anemia (41%), musculoskeletal pain (30%), rash (30%), bruising (30%), nausea (29%), fatigue (29%), hemorrhage (22%), and pyrexia (21%).

The most common Grade 3 or 4 adverse reactions (≥20%) in patients with cGVHD were fatigue (12%), diarrhea (10%), neutropenia (10%), pneumonia (10%), sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

**DRUG INTERACTIONS**

*CYP3A Inducers:* Avoid concomitant use with strong CYP3A inducers.

*CYP3A Inhibitors*: Avoid concomitant use with strong CYP3A inhibitors.

**SPECIFIC POPULATIONS**

**Hepatic Impairment** (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

Please see the Brief Summary on the following pages.

To learn more, visit [IMBRUVICAHCP.com](http://IMBRUVICAHCP.com)
Gastrointestinal disorders: Diarrhea, nausea. Abdominal pain, vomiting.

Hematologic disorders: Anemia, thrombocytopenia, neutropenia.

Infections and infestations: Pneumonia, urinary tract infection, skin infections, sinusitis.

General disorders and administration site conditions: Fatigue, peripheral edema, pyrexia, myalgia, arthralgia.

Skin and subcutaneous tissue disorders: Rash, skin infestations.

Nervous system disorders: Dizziness, headache.

Respiratory, thoracic, and mediastinal disorders: Dyspnea, cough, epistaxis.

Metabolism and nutritional disorders: Decreased appetite, dehydration.

Vascular disorders: Hypertension.

Hematologic disorders: Anemia, thrombocytopenia, neutropenia.

Infections and infestations: Pneumonia, urinary tract infection, skin infections, sinusitis.

Metabolism and nutritional disorders: Decreased appetite, dehydration.

Vascular disorders: Hypertension.

* One patient death due to histiocytic sarcoma.
IMBRUVICA® (ibrutinib) capsules

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=119)</th>
<th>Ofatumumab (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>69</td>
<td>12</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=119)</th>
<th>Ofatumumab (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
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<td>Diarrhea</td>
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<td>Nausea</td>
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<td>Stomatitis</td>
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<td>Constipation</td>
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<td>Vomiting</td>
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<td>0</td>
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<td>General disorders and administration site conditions</td>
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<tr>
<td>Pyrexia</td>
<td>24</td>
<td>15</td>
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<tr>
<td>Infections and infestations</td>
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<td></td>
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<tr>
<td>Upper respiratory tract infection</td>
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<td>11</td>
</tr>
<tr>
<td>Pneumonia</td>
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<td>10</td>
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<tr>
<td>Sinusitis</td>
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<td>9</td>
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<tr>
<td>Urinary tract infection</td>
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<td>5</td>
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<td>Skin and subcutaneous tissue disorders</td>
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<td>Rash*</td>
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<tr>
<td>Petechiae</td>
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<td>Bruises</td>
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<td>Nervous system disorders</td>
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<tr>
<td>Urticaria</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
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<tr>
<td>Contusion</td>
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<td>3</td>
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<tr>
<td>Eye disorders</td>
<td>10</td>
<td>3</td>
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</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and at Least 2% Greater in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE 2 (continued)

<table>
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<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=136)</th>
<th>Chlorambucil (N=132)</th>
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<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<tr>
<td>Cough</td>
<td>10</td>
<td>0</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Peripheral edema</td>
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</tr>
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<td>Pyrexia</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vascular Disorders</td>
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<td></td>
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<td>Hypertension*</td>
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<td>4</td>
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<tr>
<td>Nervous System Disorders</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term. The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 8: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=287)</th>
<th>Placebo + BR (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Bruising*</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>4</td>
</tr>
</tbody>
</table>

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=42)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA (N=136)</th>
<th>Chlorambucil (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Gastrintestinal reflux disease</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Bruising*</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>
Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Table 10: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with WM in Study 1118 (N=63)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic conditions</td>
<td>Neutrophils Decreased</td>
<td>44</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Neutrophils Increased</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin Decreased</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 11 and 12 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 11: Non-Hematologic Adverse Reactions in > 10% in Patients with MZL in Study 1121 (N=63)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified (including cysts and polyps)</td>
<td>Skin cancer</td>
<td>11</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

Table 12: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with MZL in Study 1121 (N=63)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic conditions</td>
<td>Neutrophils Decreased</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Neutrophils Increased</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin Decreased</td>
<td>13</td>
</tr>
</tbody>
</table>

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1115) that included 42 patients with cGVHD after failure of first line corticosteroid therapy and required additional therapy.

The most commonly occurring adverse reactions in the cGVHD trial (≥ 20%) were fatigue, bruising, diarrhea, thrombocytopenia, stomatitis, muscle spasms, nausea, hemorrhage, anemia, and pneumonia. Atrial fibrillation occurred in one patient (2%) which was Grade 3.

Twenty-four percent of patients receiving IMBRUVICA in the cGVHD discontinuation trial due to adverse reactions. The most common adverse reactions leading to discontinuation were fatigue and pneumonia. Adverse reactions leading to dose reduction occurred in 26% of patients. Adverse reactions and laboratory abnormalities described below in Tables 13 and 14 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 13: Non-Hematologic Adverse Reactions in > 10% in Patients with cGVHD (N=42)

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified (including cysts and polyps)</td>
<td>Skin cancer</td>
<td>11</td>
</tr>
</tbody>
</table>

The body system and individual ADR preferred terms are sorted in descending frequency order.

Additional Important Adverse Reactions: Diarrhea: Diarrhea of any grade occurred at a rate of 43% (range, 36% to 56%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 19%) of Grades 3 and 4 in 3% (range, 0% to 5%) of patients treated with IMBRUVICA. The median time to first onset of any grade diarrhea was 10 days (range, 0 to 67), of Grade 2 was 39 days (range, 1 to 719) and of Grade 3 was 74 days (range, 3 to 627). Of the patients who reported diarrhea, 82% had complete resolution, 1% had partial improvement and 11% had no reported improvement at time of analysis. The median time from onset to resolution or improvement of any grade diarrhea was 5 days (range, 1 to 418), and was similar for Grades 2 and 3. Less than 1% of patients discontinued IMBRUVICA due to diarrhea.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 10% of patients treated with IMBRUVICA (9% Grade 1, 1% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 81% had complete resolution and 38% had no reported improvement at time of analysis. The median time from onset to resolution or improvement was 29 days (range, 1 to 335 days).

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of IMBRUVICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hepatobiliary disorders: hepatic failure
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis
- Infections: hepatitis B reactivation

DRUG INTERACTIONS

Effect of CYP3A Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity.

Examples of strong CYP3A inhibitors include: becotecrivir, clarithromycin, cobicistat, conazapREV, rifapentine, rifaximin, ritonavir, saquinavir, and telithromycin.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% and 15-20%, respectively.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or MZL and 20 times the exposure in patients with CLL/SLL or WM administered the dose of 150 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal variations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased resorptions and post-implantation loss. The dose of 15 mg/kg/day in rabbits is approximately 2.0 times the exposure (AUC) in patients with MCL and 2.8 times the exposure in patients with CLL/SLL or WM administered the dose of 560 and 420 mg daily, respectively.

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for IMBRUVICA or any potential adverse effects on the breastfed child from IMBRUVICA or from the underlying maternal condition.

Females and Males of Reproductive Potential: Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating IMBRUVICA therapy.

Contraception: Females: Advise females of reproductive potential to avoid pregnancy while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus. Males: Advise men to avoid fathering a child while receiving IMBRUVICA, and for 1 month following the last dose of IMBRUVICA.

Pediatric Use: The safety and effectiveness of IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 905 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 21% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades) and Grade 3 or higher pneumonia occurred more frequently among older patients treated with IMBRUVICA.

Hepatic Impairment: Avoid use of IMBRUVICA in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Monitor patients for adverse reactions of IMBRUVICA and follow dose modification guidance as needed. [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information.]

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA.

Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

• Hemorrhage: Inform patients of the possibility of bleeding, and to report any signs or symptoms (severe headache, blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

• Infections: Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills, weakness, confusion) suggestive of infection [see Warnings and Precautions].

• Atrial fibrillation: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort [see Warnings and Precautions].

• Hypertension: Inform patients that high blood pressure has occurred in patients taking IMBRUVICA, which may require treatment with anti-hypertensive therapy [see Warnings and Precautions].

• Second primary malignancies: Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].

• Tumor lysis syndrome: Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions].

• Embryo-fetal toxicity: Advise women of the potential hazard to a fetus and to avoid becoming pregnant during treatment and for 1 month after the last dose of IMBRUVICA [see Warnings and Precautions].

• Inform patients to take IMBRUVICA orally once daily according to their physician’s instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see Dosage and Administration (2.1) in Full Prescribing Information].

• Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see Dosage and Administration (2.8) in Full Prescribing Information].

• Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

• Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

• Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration [see Adverse Reactions].

Active ingredient made in China.

Distributed and Marketed by: Pharmacyclics LLC
Sunnyvale, CA USA 94085
and Marketed by: Janssen Biotech, Inc.
Horsham, PA USA 19044
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PRC-03045
Serum Protein Signature Predicts Survival in Patients With Melanoma Receiving Anti-PD-1 Therapy
Jaime Rosenberg

**A PRETREATMENT SIGNATURE OF** proteins predicted survival in patients with metastatic melanoma receiving programmed cell death protein 1 (PD-1)–blocking antibodies, according to a December 2017 study published in *Cancer Immunology Research.*

Prior clinical results in patients with metastatic melanoma being treated with the PD-1 inhibitors nivolumab and pembrolizumab have led to substantial improvements in progression-free survival (PFS) and overall survival (OS). According to authors led by Jeffrey S. Weber MD, PhD (see Cover Story), there also have been efforts made toward determining the utility of programmed death ligand-1 (PD-L1) expression on tumor and/or immune infiltrating cells, as measured by immunohistochemistry.

"Correlations between PD-L1 expression and outcome with PD-1/PD-L1 antibodies have been observed in many studies, but melanoma patients with negatively stained tumors may still benefit from anti-PD-1 therapy," the authors wrote. "A serum-based pre-treatment test of circulating proteins would not require tissue, and if found to be associated with a favorable response to PD-1 blocking antibodies, would be clinically useful."

The authors conducted the test by collecting sera from 6 sample sets for test development and validation:

• A development set of 119 patients with stage IV melanoma prior to treatment, in which the efficacy of nivolumab monotherapy at 1, 3, and 10 mg/kg with or without a multi-peptide vaccine was evaluated
• 3 validation sets of 101 patients receiving nivolumab or pembrolizumab
• A validation set of 48 patients receiving ipilimumab

The sera were obtained with a matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry. These data, along with clinical data, were used to identify patients with better or worse outcomes. The test, developed with the Diagnostic Cortex™ platform, was based on mass spectrometry analysis of patient serum samples. A signature consisting of 209 proteins or peptides was associated with OS and PFS in a multivariate analysis. For the development set, the test classified 34 patients (29%) as “sensitive” and 85 (71%) as “resistant.” Both OS and PFS showed significant separation (P=0.002 and .016, respectively) by test classification, with substantial effect sizes for each (hazard ratios [HRs] of 0.37 and 0.55, respectively). Patients deemed “sensitive” had a 2-year survival rate of 67%.

The authors found that the test performance across validation cohorts was consistent with the development set results. Results of the pooled analysis showed significantly better OS for patients classified as “sensitive” compared with patients classified as “resistant” (HR, 0.15; 95% CI, 0.06-.40; P=.001). The ipilimumab-treated validation set demonstrated a significant difference in OS between sensitive and resistant groups (HR, 0.40; P=.004).

"The serum test described herein might identify patients expressing the ‘sensitive’ serum classification that have long overall survival with PD-1 blockade alone or with the addition of ipilimumab to nivolumab,” the authors concluded.

**REFERENCE**

Increased CD8+ TIL Counts Linked to Prolonged Survival in Patients With Certain Ovarian Cancers
Jaime Rosenberg

**EPITHELIAL OVARIAN CANCER (OC)** is responsible for 14,000 deaths each year in the United States, and although initial remission is often achieved, patients often relapse and succumb to the disease. Increasing CD8+ tumor-infiltrating lymphocytes (TILs) in several OC histotypes is associated with an increased rate of survival, according to a study published in *JAMA Oncology.*

"Cytotoxic CD8+ TILs participate in immune control of epithelial ovarian cancer," the study authors wrote. "However, little is known about prognostic patterns of CD8+ TILs by histotype and in relation to other clinical factors."

The authors assessed a prospective cohort of 5577 women with a primary diagnosis of epithelial ovarian, peritoneal, or fallopian tube cancer. Of the 5577 women, 5078 had tumors of the 5 major histotypes: high-grade serous OC (HGSOC), endometrioid OC (ENOC), clear cell OC (CCOC), mucinous OC (MOCC), and low-grade serous OC (LGSOCC). The patients were followed until death from any cause. Tumor specimens were taken from an initial debulking surgery, formalin-fixed, paraffin-embedded, and arranged on tissue microarrays.

Epithelial CD8+ TILs were examined using a 4-tiered scoring system. Of the HGSOC cases, 83% had evidence of CD8+ TILs, with lower rates seen in LGSOCC (73%), ENOC (72%), CCOC (52%), and MOC (51%).

The results showed a strong association between increasing levels of CD8+ TILs and prolonged survival in HGSOC cases. The median survival was 2.8 years for women negative for CD8+ TILs, 3 years for low levels, 3.8 years for moderate levels, and 5.1 years for high levels. According to the authors, at the extremes, women with high levels of CD8+ TILs had a 43% reduced risk of death compared with women negative for CD8+ TILs. Increasing levels of CD8+ TILs were also linked to prolonged survival for women with ENOC and MOC.

Among HGSOCs, CD8+ TILs were favorable regardless of the extent of residual disease following cytoreduction, known standard treatment, and germline *BRCA1* pathogenic mutation. However, they were not prognostic for *BRCA2* mutation carriers.

"These large-scale analyses show that CD8+ TILs vary by histotype with HGSOC tumors having the highest levels and a strong association with survival, regardless of extent of residual disease or first-line chemotherapy treatment," the authors wrote. "We showed for the first time that CD8+ TILs in HGSOC cases with germine *BRCA2* mutations may not be associated with survival. Finally, we found that ENOC and MOC tumors show trends associating CD8+ TILs with survival time and that COCC do not show these trends.”

The authors indicated that a clinically applicable scoring system for CD8+ TILs should be developed and incorporated into clinical trials.

**REFERENCE**
Sarcopenia and Inflammation Associated With Increased Risk of Death in Patients With CRC

Jaime Rosenberg

PRE-DIAGNOSIS INFLAMMATION WAS ASSOCIATED with at-diagnosis sarcopenia (low skeletal muscle mass), and the combination of the 2 nearly doubled the risk of death in patients with nonmetastatic colorectal cancer (CRC), according to a study published in JAMA Oncology.

Sarcopenia and an elevated neutrophil-to-lymphocyte ratio (NLR, a measure of systemic inflammation), have been increasingly recognized as 2 novel prognostic indicators across cancer types, according to the authors. Sarcopenia can be used to predict adverse outcomes such as poor surgical outcomes, treatment toxicity effects, and reduced survival. Similarly, NLR values are utilized to predict treatment response.

“Whereas both sarcopenia and inflammation can be evaluated with existing clinical data and may be modifiable, the relationship between these 2 factors and their independent associations with survival are not well studied,” the authors wrote.

The authors studied 2,470 patients from the Colorectal Cancer: Sarcopenia, Cancer, and Near-term Survival (CSCANS) cohort, which included Kaiser Permanente Northern California (KPNC) health plan members who were diagnosed with stage I to III CRC between 2006 and 2011. All participants underwent surgical resection and had abdominal computed tomography (CT) scans at diagnosis. Using the scans, the authors measured skeletal muscle index. Sarcopenia was defined as less than 52 cm²/m² for normal or overweight men and less than 38 cm²/m² for normal or overweight women, and less than 54 cm²/m² and less than 47 cm²/m² for obese men and women, respectively.

Systematic inflammation was measured by NLR from routine blood tests, and the authors averaged all available NLR measures from the 24 months prior to diagnosis. The mean number of NLR measures was 3, and was characterized using standard cut-offs to define normal inflammation as less than 3, moderate inflammation as 3 to less than 5, and high inflammation as 5 or higher.

The results showed that patients with a higher NLR in the 24 months prior to their diagnoses had less favorable values for all other markers of systemic inflammation: higher platelet-to-lymphocyte ratio, lower lymphocyte-to-monocyte ratio, and lower serum albumin level.

The prevalence of an NLR of 3 or greater and sarcopenia were 46% (n = 1133) and 44% (n = 1078), respectively. Over a median of 6 years of follow-up, there were 656 deaths, 357 of which were from CRC. Increasing NLR associated with sarcopenia in a dose-response manner: compared with patients with NLR of less than 3, the odds ratios (ORs) for sarcopenia were 1.35 (95% CI, 1.18-1.67) for NLR of 3 to less than 5 and 1.47 (95% CI, 1.16-1.85) for NLR of 5 or greater (P for trend across categories, <.001).

Results also showed that an NLR of 3 or greater and sarcopenia independently predicted overall and CRC-related death. Patients with both sarcopenia and an NLR of 5 or greater had a double the risk of death overall (HR, 2.12; 95% CI, 1.70-2.65) and CRC-related death (HR, 2.43; 95% CI, 1.79-3.29).

“Both sarcopenia and high NLR were independent prognostic indicators in nonmetastatic CRC,” the authors concluded. “If our findings are confirmed by additional studies, these 2 biomarkers are already collected in routine care and thus have high potential for use in clinical prognostication.”

REFERENCE

CLINICAL/MANAGED CARE UPDATES

The Impact High OOP Costs Have on Patients Filling Prescriptions for Oral Cancer Drugs

Laura Joszt, MA

PATIENTS WITH CANCER MAY HAVE more options for oral cancer medications, but high out-of-pocket costs still present a barrier to access, according to a new study in JAMA Oncology.

Researchers reviewed claims from 2014 to 2015 from a large, proprietary, integrated database that included Medicare and commercial insurance enrollees for 36 oral anticancer agents. They looked at claim reversal (patients failing to purchase an approved prescription), delayed initiation, and abandonment.

The overall abandonment rate was 18% and rates of claim reversal ranged from 13% to 67% depending on the out-of-pocket (OOP) costs. The study found that 10% of patients who had to pay less than $10 did not pick up their prescription, while 32% of those who had to pay between $100 and $500 and nearly 50% of those who had to pay more than $2000 did not pick up their prescription.

“Patients in our study were facing a new cancer diagnosis or a change in their disease that required a new treatment. Imagine leaving your doctor’s office with a plan, ready to start treatment, only to find you can’t afford it,” lead author Jalpa A. Doshi, PhD, a professor in the Perelman School of Medicine at the University of Pennsylvania, and director of Value-Based Insurance Design Initiatives at the Leonard Davis Institute’s Center for Health Incentives and Behavioral Economics, said in a statement. “It adds more stress at what is already a stressful and scary time.”

The researchers also found that the relationship between high OOP costs and patients not filling their prescriptions was consistent across cancers, even for those that have treatments that significantly extend life. Patients with high OOP costs who did fill their prescriptions were more likely to delay it. With oral drugs, more of the medication’s cost is passed to the patient and complete payment is due upfront, which increases the risk of delayed access or abandonment.

The authors determined that if patients currently paying between $50 and $100 for prescription were bumped up to a higher cost category and were responsible for $100 to $500 instead, that the abandonment rates would actually double.

“This shows the importance of discussing financial barriers up front, during conversations about treatment options, even with patients who don’t raise concerns,” Doshi said. “Patients may not be aware of how expensive their prescriptions will be, and physicians may not realize that a patient has opted not to fill the prescription.”

REFERENCE

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www.amjc.com/about/ebo
Average Profit Margin on Oncology Drugs for 340B Hospitals Nears 50%

Jaime Rosenberg

THE AVERAGE PROFIT MARGIN on oncology drugs purchased by hospitals through the 340B program increased to 49% in 2015, subsequently leading to price pressure on cancer drugs, according to new study findings.

"The Oncology Drug Marketplace: Trends in Discounting and Site of Care," commissioned by the Community Oncology Alliance (COA) and conducted by Berkeley Research Group, expanded upon previous research on the 340B program and assessed the impact the program had on the shift to more expensive hospital outpatient settings for cancer care; the scale of statutory discounts on oncology drugs, specifically 340B drugs; and the part these discounts play in drug pricing.

Currently, nearly half of all cancer patients are treated in hospital outpatient facilities, up from 23% in 2008. While limited research exists on the impact that this shift in site of care has on quality of care and patient outcomes, there is significant evidence of its role in overall healthcare cost increases, according to the authors of the study.

“The continued shift of oncology care to the hospital outpatient setting, combined with increased rates of cancer and rising drug prices, is setting the stage for higher overall costs of oncology care,” the authors wrote.

The authors developed an analysis by utilizing 2 sets of oncology drugs and Medicare fee-for-service claims from 2008 to 2016. Using a combination of IMS wholesale acquisition cost (WAC) sales data from 2010 to 2015 and publicly available pricing data, the authors conducted a financial analysis of sales, discounts, rebates, and 340B margins on a subset of the separately payable oncology drugs that accounted for 85% of total Medicare Part B oncology drug reimbursement in 2015.

The study had 4 main findings:

1. **340B hospitals have a clear financial incentive to expand oncology services.** From 2011 to 2016, the average discount of a drug’s list price for Medicaid increased from 44% to 51%. The authors estimate that the average 340B discount from WAC increased from 54% in 2010 to 63% in 2015, which is responsible for keeping the 340B price consistent over that time period. Medicare reimbursement for physician-administered drugs equals 106% of a drug’s average sales price (ASP).

2. **340B hospitals receive over one-third of all Part B oncology drug reimbursement.** Between 2008 and 2016, the percentage of oncology drug reimbursement to 340B hospitals has more than tripled. According to the authors, there are multiple factors that contributed to the growth: new entity enrollment, growth in contract pharmacy, and expansion of oncology services by 340B hospitals. During the same period, the percentage of oncology drug reimbursement to community oncology practices has declined from 72% to 49%.

3. **A disproportionate share of the shift in site of care is attributable to 340B hospitals.** The authors analyzed enrollments of 2 cohorts between 2008 and 2016: hospitals that were continuously enrolled in 340B and hospitals that were not enrolled. By 2016, the 340B cohort accounted for over 920,000 oncology claims, a 38% greater growth than the non-340B cohort. “What we saw was that the majority of the growth has come out of existing hospitals through internal growth or acquiring practices,” said Ted Okon, executive director of COA.

4. **Between 2010 and 2015, statutory discounts and rebates paid by manufacturers have almost tripled and put upward pricing pressure on drugs.** In 2010, the statutory discounts and rebates on oncology drugs included in the analysis were approximately $1 billion and accounted for 7.4% of total gross sales for these drugs. By 2015, statutory discounts and rebates on the same set of drugs surpassed $3 billion and accounted for 14.4% of total gross sales for these drugs. The primary driver of this was the 340B program.

There is a lot that needs to be done, explained Okon, and CMS’ final rule is a step in the right direction. Last month, CMS finalized reform that will adjust payments for the 340B program; the Hospital Outpatient Prospective Payment System (OPPS). The program will adjust payment for drugs purchased through the 340B program to the ASP minus 22.5%, a change from the current rate of plus 6%.

CMS said that the rule will help lower the cost of the prescription drugs and the savings from this will be redistributed equally to hospitals covered by OPPS. In an attempt to create more transparency, 2 modifiers will be put in place in order to identify whether a drug has been purchased under the 340B program. These changes took effect on January 1, 2018.

“What you need next is Congress to shine the light on transparency,” said Okon. “340B is a black hole right now; we have no idea what goes on. Hospitals should be held to the same level of accountability that these federal grantees are.”

The 340B program, which was initiated 25 years ago, requires drug manufacturers participating in the Medicaid Drug Rebate Program to provide a discount to covered safety-net health providers. The program enables these entities to stretch scarce federal resources as far as possible to reach more low-income patients who are uninsured and provide more comprehensive resources.
CONTINUED

The Clinical Trial and the Patient’s Voice: “I’m Extremely Lucky to Be Alive”

Mary Caffrey

For Hall, the idea of immunotherapy in a pill was a revelation. But based on experience, he still saw taking part in a clinical trial as a big responsibility—one with long days and travel at the outset for tests at Florida Cancer Specialists’ research facility in Sarasota, some 60 miles from his home in Dunedin. It’s worth it, however. Despite the adverse effects he experienced in a previous trial, and all the driving, Hall knows that he’s beaten the odds.

He is serious about his part in the scientific process. “You have to keep a log,” Hall says, because researchers want to know exactly when medications are taken. “You have to be honest.” And there’s much a person can’t consume, ranging from vitamins and herbal supplements to Florida grapefruit.

It’s not just about what the trials have done for him. Hall knows what he’s doing is part of something bigger, and the prospect of helping younger cancer patients motivates him to take part in early-phase studies. “I’ve been married 3 times so I’m not good at that,” he says. “I’m 74 years old. I figure if I can participate in research to help someone else, that’s fine with me. I have young friends with cancer, and my heart bleeds for them.”

Didn’t know how to spell lymphoma at diagnosis

It’s been nearly 20 years since Robert Mesloh noticed what appeared to be a small cyst on his right temple one morning while shaving. He was on a business trip in Singapore, and upon returning home to New Jersey he went to his family doctor, who referred him to a dermatologist, who sent him to a surgeon to have it removed. Two weeks later came the pathology report and a late-night phone call about a term Mesloh had never heard: follicular indolent non-Hodgkin lymphoma.

“I didn’t even know how to spell lymphoma, much less that it was a cancer,” Mesloh says. “But then, being a double type A personality, I had to find out as much about it as I could.”

It was the early days of the internet, but Mesloh didn’t want to rely only on that, so he connected with the group that would become the Lymphoma Research Foundation (LRF). In time, he became an LRF ambassador, testifying before Congress, traveling to annual meetings, and interacting with researchers from around the world. He’s now retired and has moved from Parsippany, New Jersey, to The Villages, Florida, but his charitable work continues.

Through the LRF, Mesloh serves as a consumer representative—a patient voice—on one board that awards research grants for cancer prevention and research within the state of Texas, and on another board that awards grants on behalf of the Department of Defense.

His activism, and his own deep dive into understanding lymphoma, have shown Mesloh how fortunate he was to initially find an excellent oncologist, Charles Farber, MD, PhD, who not only specialized in lymphoma but also excelled in explaining the available treatment options, limited as they were at the time.

“When I had my original diagnosis in 1998, I was what they called pre-stage I,” Mesloh says, and there was a 12% chance that the surgery had removed all the cancer; Mesloh also received radiation. Five years later in 2003, he had a recurrence in the abdomen. In that span, a “miracle” therapy had arrived: the regimen known as R-CHOP (rituximab with cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine sulfate [Oncovin], and prednisone) had made a splash at the 2002 meeting of the American Society of Hematology. After treatment with R-CHOP, Mesloh received rituximab maintenance therapy for 2 years.

“Currently, knock on wood, I’m still in complete remission,” he says.

Mesloh was among the first group of patients to gain access to R-CHOP under general availability. Having Farber as his oncologist made all the difference, and Mesloh encourages lymphoma patients to seek a specialist. “Back in 1998, there wasn’t very much that was available,” he says, likening the era to the Dark Ages, compared with what Mesloh sees today as the Golden Age of lymphoma research.

When he was diagnosed, Mesloh says, Farber told him there were 3 to 4 types of Hodgkin lymphoma and 22 to 24 types of non-Hodgkin lymphoma. Now, “to date, we know categorically, there are 80-plus types of non-Hodgkin’s lymphoma,” he says. The completion of the human genome project and other technological advances have yielded more details about cancer subtypes, human DNA, and cancer-cell DNA, and each subtype requires a different approach.

Mesloh is keenly aware how timing worked in his favor. If his lymphoma had shown up just a few years earlier, he would have missed the broader availability of rituximab and R-CHOP—specifically for this 1 form of the 80-plus types of lymphoma.” At one point, Mesloh may not have known how to spell lymphoma, but he can now explain in detail how a monoclonal antibody attaches to the antigen on a cancer cell and “choke it, so it can’t get any more nourishment.

Still, those people treating Mesloh have stopped short of saying he is cured. “To this very day, I still think about it, though it’s not in the forefront of my mind,” Mesloh remarks.

Could “set the clock” by symptoms from study drug

Within weeks of his 2013 diagnosis, Hall was enrolled in a phase 2 clinical trial involving folic acid and oxaliplatin (FOLFOX) and tivantinib, under the care of Sarasota-based researcher Manish Patel, MD. That worked for 2-and-a-half years,” Hall says. (The

—Wesley Hall, 3-time clinical trial participant

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—Wesley Hall, 3-time clinical trial participant
By the end of 2015, Hall’s cancer had progressed, so he was taken off the trial and put on regular chemotherapy, staying closer to home for care. In January 2016, Patel offered Hall an opportunity for another clinical trial, this time a phase 1 study involving the immunotherapy durvalumab, the programmed cell death ligand–1 inhibitor that a year later would be granted accelerated FDA approval for certain patients with metastatic urothelial carcinoma.7

Hall had heard about adverse events (AEs) from immunotherapy, but durvalumab turned out not to be the problem, although he ran a high fever of about 104 degrees for the first month or so as his immune system adjusted to the treatment. That didn’t bother him. The targeted therapy he took alongside the durvalumab was another story. The other drug, an as-yet unnamed oral WEE1 kinase inhibitor,7 caused intestinal AEs so toxic and predictable, Hall says, that “I could set the clock by when the symptoms were going to start [and] when they were going to stop.”

According to trial information from AstraZeneca, the WEE1 kinase inhibitor is designed to target a protein that plays a role in cell cycle progression and protein phosphorylation—a pharmacologically targetable mechanism that lets cells respond to conditions around them.9 Hall told EBO™ that at the time he stopped taking the combination in November 2016—when a stomach mass reappeared after 11 months—he was the only person who had stuck with the WEE1 kinase inhibitor beyond 2 months. The trial is still recruiting patients, and notes on ClinicalTrials.gov reveal that the drug was so difficult to tolerate that the original dosing schedule was amended; it now includes 2 new schedules that add dexamethasone on the first day of the WEE1 kinase inhibitor, because patients on the first schedule experienced “dose-limiting toxicity.”9

In early 2017, Hall returned to Jooma’s practice just minutes from home, where he started on a series of radiation and chemotherapy treatments: carboplatin plus taxol. “That kind of killed everything,” Hall says. By April 2017 he had no signs of cancer in his stomach, but once again he’d experienced neuropathy. That is why when a new tumor emerged in January 2017, Jooma and Patel wanted to try “something my body hadn’t already seen,” as Hall puts it.

“The research grants that are coming through, actually for all forms of cancer, are looking down at the molecular level of how to attack the specific forms of cancer,” Mesloh says. Studies that look to use older medications in new ways, along with genetic testing that allows for personalized medicine in cancer care, are gaining traction. By these developments, he says, “I’m very encouraged.”

Less encouraging, Mesloh says, are frustrations like the “archaic system of billing,” including the disparity between the ways infusion and oral medications are treated in some health benefit plans. (Oral therapies are sometimes treated as a pharmacy benefit with high out-of-pocket costs for patients, while infusion therapy is treated as a medical benefit.) There’s also not enough progress on sharing information among institutions, despite much talk of doing so during former Vice President Joe Biden’s Moonshot initiative.11

The biggest challenge Mesloh hears about is the tiny share of patients willing to take part in clinical trials. “In the United States, only about 5% of our population which are diagnosed with a cancer will go on a clinical trial. That disappoints me.” —Robert Mesloh, 20-year cancer survivor, ambassador, Lymphoma Research Foundation

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To bring precision medicine to its potential, that population who are diagnosed with a cancer will go on a clinical trial, to be followed by radiation. Through it all, Hall’s optimism shines through as he described “seeing my old friends,” at his appointment. He sounded hopeful about the next chapter of his journey, which would start in just 12 days.

His trust in Jooma is complete. “I’m confident he will take good care of me.”

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Ipilimumab did not work for everyone. But when it did, patients with the deadliest form of skin cancer—who would have survived just months on chemotherapy—now survived years. A 2013 article Weber coauthored found survival rates of 37.7% to 49.5% at the 4-year mark for treatment-naive patients in phase 2 trials.4

Much has changed since then, both for immunotherapy and for Weber, who has been a leader in bringing basic research into clinical practice for more than 20 years. In November 2015, he left the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida, to become deputy director of the Laura and Isaac Perlmutter Cancer Center at New York University Langone Medical Center.5 As Weber points out, today there are more checkpoint inhibitors—including nivolumab (Opdivo, BMS)6 and pembrolizumab (Keytruda, Merck)7—approved for many more cancers, such as non–small cell lung cancer, renal cell cancer, head-and-neck cancers, Hodgkin lymphoma, and colon cancer.8 In the case of ipilimumab, the target is cytotoxic T-lymphocyte antigen–4. Both nivolumab and pembrolizumab target the programmed cell death 1 (PD-1) protein.

“I think people are becoming more aware of the issues surrounding immune-related adverse events. There’s a huge gap in how to manage them.”

— Jeffrey S. Weber, MD, PhD

In a new interview with Evidence-Based Oncology™, Weber discussed developments in the past year that are rapidly changing immuno-oncology treatment approaches in melanoma. Ipilimumab’s place in the melanoma armamentarium is shifting, thanks in part to research Weber presented in the past year but also because of new combinations in the pipeline. Ipilimumab will still be used, he said, but it will likely be used in new and different ways. And new cost issues are on the horizon, as the prospect of triple therapy is no longer something of the imagination. Not long after the interview, on December 20, 2017, the FDA approved the use of nivolumab for adjuvant treatment of melanoma,9 on the heels of Weber’s presentation of results of the CHECKMATE 238 study at the European Society for Medical Oncology (ESMO). The study found that at 18 months, the difference in relapse-free survival was 66% for those taking nivolumab compared with 53% for ipilimumab, with far fewer immune-related adverse events (AEs) for those taking nivolumab.10 Also in December, Weber was senior author for a study in Cancer Immunology Research showing that a test based on a protein signature associated with metastatic melanoma outcomes can predict patient survival and help oncologists decide which PD-1–blocking antibodies are appropriate for which patients.11 The findings support Weber’s discussion of the growing importance of biomarkers in steering very expensive therapies to patients who will respond to them and for figuring out in advance which patients won’t respond.

**New Standard for Advanced Melanoma?**

Weber and others see a big change ahead: Investigators at ESMO presented results for a combination of pembrolizumab and epacadostat (Incyte), an inhibitor of the enzyme indoleamine 2,3-dioxygenase-1, or IDO1. The overall response rate of 56% and median progression-free survival (PFS) of 12.4 months in the phase 1/2 trial,12 combined with AE rates that are better than the ipilimumab–nivolumab combination, suggest to Weber that a changing of the guard could be on the way in advanced melanoma.

“Based on all the phase 1/2 data, it looks pretty promising,” Weber said. “I would predict if pembrol–epacadostat has anywhere near a 12-month PFS and a 50-plus percent response rate, I think people will embrace it,” noting that the ipilimumab–nivolumab combination will become second-line treatment. (Indeed, reports of the early pembrolizumab–epacadostat results have fueled speculation about the future of the Bristol-Myers Squibb [BMS] combination but also about epacadostat and nivolumab.13)

“You’ll need to look for new [ipilimumab] combinations. Ipilimumab has been kind of ignored in terms of drug development in the last 5 years. But now, all of a sudden [ipilimumab] becomes an important second-line treatment,” Weber said. He rattled off a list of potential combinations: ipilimumab–epacadostat, ipilimumab plus talimogene-laherparepvec, or T-VEC; ipilimumab and anti-lymphocyte activation gene-3, known as LAG-3.

“[Ipilimumab] becomes an important second-line treatment,” Weber said. “It will be good for patients, because if the pembrol–epacadostat trial pans out, it will become adopted. I’m sure that’s the way it will go in the community.”

**AEs and a “Provocative Question”**

The prospect of an alternative to ipilimumab–nivolumab has attracted widespread attention in part because so many patients suffer reactions. “The initial [ipilimumab–nivolumab] combo was, and is, pretty darn toxic,” Weber said. “Whether you give, [the drugs] consecutively—one after the other as we did in a prior study—or concurrently, you have a 50% to 60% rate of immune-related adverse events. That’s pretty serious.”

And yet, Weber said, there’s been “surprisingly little” research on the etiology and prediction of immune-related AEs over the past decade. But this could be changing. In 2017, Weber noted, the National Cancer Institute (NCI) included an item on this very issue in its Provocative Questions, which are items that

**Bibliography**

investigators are asked to address in grant requests. Precisely, the question is:

“What are the predictive biomarkers for the onset of immune-related adverse events associated with checkpoint inhibition, and are they related to markers for efficacy?”

“I think people are becoming more aware of the issues surrounding immune-related adverse events,” Weber said. “There’s a huge gap in education in how to manage them.” He described a patient he had recently seen who had gone 2 weeks with undiagnosed hypophysitis, an inflammation of the pituitary gland that is a known AE for patients being treated with ipilimumab. The patient’s oncologist had missed it.

As checkpoint inhibitors become approved for other cancer indications, this will become a bigger issue, Weber said. “You’re going to see a lot of approvals coming through in the next couple of years. More and more doctors will be using these drugs in the community. So there will be a big need for education.

“It’s a 2-part process: People will become more experienced; with experience comes some level of expertise. But if your average community physician is treating just a handful [of these] patients a year, experience isn’t going to help that much,” Weber said. “It’s going to take education.”

When Can Patients Stop Immunotherapy?

“That’s an open question, which will be difficult to answer,” Weber said. As patients live longer, however, the question of how long patients should stay on immunotherapy will come up more frequently. The answer isn’t obvious, he said, because it’s not the type of question investigators with funding from the NCI have typically studied—but it’s nonetheless an important one. Weber cited an abstract presented at the annual American Society of Clinical Oncology meeting in 2016 by Caroline Robert, MD, PhD, that found that patients in the KEYNOTE-001 trial who stopped pembrolizumab because of toxicity continued to receive treatment benefits.

“That, I think, will convince people that they should feel comfortable taking patients off [therapy], either after a year or 2 years. Certainly, I think patients will come off by 2 years,” Weber said, although he acknowledged it’s not an easy call. “I tell people if they’ve been on a year and they’ve had a response and the response is stabilized, they should feel comfortable coming off. Now, that’s a tough sales pitch. Imagine you’re the patient and I’m telling you it’s OK to come off a therapy when you’ve had a great response. People get a little concerned about it.”

Considering the chronic AEs, Weber would advise his melanoma patients to stay on immunotherapy “not less than 1 year, not more than 2 years.”

Can Chimeric Antigen Receptor (CAR) T-Cell Successes Seen in Leukemia and Lymphoma Occur in Solid Tumors?

CAR T-cell therapy in solid tumors has been “a huge disappointment,” Weber said, but that starts with the mechanism: “You need a cell surface molecule,” he said. “The CAR T is a fusion of the antigen-recognition region of the antibody with the T-cell transduction molecule. Other than the hematologic malignancies, there aren’t too many dispensable molecules that are present on cells that you can use as a target. In other words, you have too many off-target side effects when you have solid tumors doing CAR strategies.”

Weber noted a promising strategy involving a folate receptor with ovarian cancer, “but apart from that, I think it’s going to be a very difficult scenario.”

Optimism in Payer Coverage, but Triple Therapy Awaits

Weber said his patients at Langone have not had problems gaining coverage for immunotherapy. Not only is the system smooth at his institution, but there are differences from region to region with Medicare—and he finds things better in New York than he did in Florida. “With recent therapies, there have not been any issues at all,” he said. “One nice thing is the big companies like Merck and BMS have tended to have patient assistance programs,” so even though he just presented data on adjuvant nivolumab last fall, “if you can’t get insurance [coverage], you can get it through patient assistance. So I think that’s a good thing.”

Still, the prospect of triple combination therapy concerns him. “Now, we’re talking the kind of money that we were talking about for CAR T cells. And that really flipped everybody out,” he said. The announced price of the first CAR T-cell therapy, tisagenlecleucel (Kymriah, Novartis), was $475,000, although Weber noted reports that Novartis was negotiating an outcomes-based agreement with the CMS that would call for Medicaid to pay only if the treatment worked.

As immunotherapy moves into the adjuvant population, the math becomes more challenging for payers and institutions if “the best you can do is
treat 2 patients to benefit 1," Weber said. That's why the development of better biomarkers becomes so important. “You’d rather know who are the patients who are going to be cured” and which ones won’t. Thus, targeting the right patients to treat is a huge research focus right now, he said.

“This is the story of where we’re heading,” Weber said. Without better biomarkers, “even if you have the perfect therapy, you're still going to be treating twice as many patients as you need to.”

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A study published by the *Journal of Clinical Oncology* last fall found that Herceptin’s price had climbed 78% between 1996 and 2012, although a commenter said the study failed to account for the effects of the 340B drug discount program.2 But the situation could be changing. The *FiercePharma* report projected that Herceptin sales would fall to $3.98 billion by 2022.3 Early in 2018, at least 1 national payer, Humana, has moved Herceptin to a less favorable formulary position in some markets; at press time, a spokesperson for the insurer had not responded to inquiries from *Evidence-Based Oncology*™ (*EBO™*) whether the change was related to the anticipated availability of Ogivri.

“I think biosimilars for trastuzumab in general are an incredibly important advance,” Hope Rugo, MD, clinical professor in the Department of Medicine and director of Breast Oncology Clinical Trials at the University of California, San Francisco, said in an interview with *EBO™*. She conducted a clinical trial of Ogivri and made a presentation in support of the drug on behalf of Mylan and Biocron before the FDA’s Oncologic Drugs Advisory Committee.

“The reduced cost will improve the pool of money available for new agents as they come out, because we can’t continuously just increase and increase costs. This way, for us, where we have insurance, [it] will allow insurers to potentially continue to insure patients, and also to provide the funding for new agents when they come out. For the rest of the world, it will allow people access to trastuzumab because there will be competition in terms of providing the drug at a lower price.”

**A “Milestone” in Breast Cancer Treatment**

When Herceptin was approved by the FDA in September 1998, it was the first treatment of its kind: a targeted therapy, in this case for patients with HER2-overexpressing metastatic breast cancer. It was approved as a single agent for those who have received at least 1 prior chemotherapy regimen for metastatic disease; or, in combination with paclitaxel, for those who have not received prior treatment for their metastatic disease.1 Then, in 2006, Herceptin was approved for use in the adjuvant setting—for women who had received surgery or radiation for localized breast cancer—with the goal of preventing recurrence.12

As Jose Baselga, MD, and co-authors noted in 2006, 4 distinct trials involving trastuzumab in the adjuvant setting for early breast cancer showed that the drug reduced the risk of 3-year recurrence by about half, marking a “milestone” in the treatment of women with HER2-positive disease.18

These developments resulted in the National Comprehensive Cancer Network including HER2 testing and the use of the targeted agent Herceptin in their guidelines for treatment of early breast cancer back in 2005, and it has remained the standard of practice ever since.11

However, the cost of 12 months of adjuvant trastuzumab therapy, the standard duration of treatment, as well as the cost associated with indefinite use in a metastatic setting, raises questions of patient access to this life-saving drug.

In 2012, the FDA approved pertuzumab (Perjeta), which was designed for use in combination with Herceptin. Herceptin and Perjeta are aimed at different regions of the HER2 receptor, improving chances of survival.12

Peter Clark, MD, a practicing oncologist and chair of the Cancer Drugs Fund of the National Health Service in the United Kingdom, said that Perjeta, in combination with chemotherapy and Herceptin, provides a 16-month survival advantage in breast cancer, and provides patients “a whoppin’ benefit, but it will cost a fortune.”11

In the United States, this combination therapy was likely to cost about $900 per monthly dose until they reach their yearly OOP limit, for a treatment that was previously on a preferred formulary tier.8

A 2015 report from the American Society of Clinical Oncology estimated the global cost of cancer at $1.16 trillion.15 This price tag includes not only drugs but the costs of diagnosis, radiotherapy, imaging, pathology, surgery, and end-of-life care. Richard Sullivan, MD, PhD, director of the Kings Institute of Cancer Policy and professor, Cancer Policy & Global Health, King's College London, said that medicines account for just 4% to 5% of total improvements in patient outcomes, with most control and cure through surgery and radiotherapy, yet medicines dominate public policy and media attention.9

**Will Biosimilars Offer Relief in Pricing?**

Approval of Ogivri comes after the FDA’s Oncologic Drugs Advisory Committee voted unanimously in July 2017 to approve the biosimilar for all indications of the reference, Herceptin.16 When FDA granted final approval in December, Ogivri became the first biosimilar approved in the United States for the treatment of breast cancer or stomach cancer and only the second biosimilar approved in the United States for the treatment of any cancer.

“The approval of Ogivri represents a monumental achievement for Mylan to increase patient access to biosimilars and deliver significant savings to the US healthcare system. It will allow us to bring this important biosimilar—the first of its kind—to market in the [United States], expanding cancer patient access to more affordable treatment,” Mylan chief executive officer Heather Bresch said in a statement. “As one of the nation’s leading suppliers of cancer medicines, Mylan is excited to add to our portfolio a product representing a new generation of targeted therapies that have radically changed the way the disease is treated.”17

While biosimilars offer promise for cost savings, results have been slow to materialize. “Many of us have been disappointed by the economic savings we’ve seen from biosimilars so far,” said FDA Commissioner Scott Gottlieb, MD, during his confirmation hearing before the Senate Health, Education, Labor, and Pensions Committee. “But I do think there’s a lot of opportunity for [biosimilars] to have meaningful impact on consumers and spending going forward.”11

Although biosimilars usually provide patients with up to 15% cost savings for these life-saving treatments, the US price for Ogivri has not yet been announced. When Biocron launched the trastuzumab biosimilar in India in 2014, the reported savings compared with the reference product was 25%.19

FDA approval of Ogivri followed Mylan’s settlement with Genentech and Roche to bring the biosimilar to the market, but those terms have not been made public.20 While a precise arrival date of Ogivri is not known, a Barclays analyst projected it to be in 2019.21

**Response From Payers, Patients**

Herceptin has no competitor in the United States, but that did not stop Humana from reclassifying Herceptin from a preferred drug to a nonpreferred drug in some Florida markets for 2018.

*Becker’s Hospital Review* said some policyholders report the change has left them with 20% copays, translating to out-of-pocket (OOP) costs of more than $900 per monthly dose until they reach their yearly OOP limit, for a treatment that was previously on a preferred formulary tier.8

In a statement to *Becker’s*, Humana said, “We recognize the importance of medications like Herceptin. Herceptin remains covered in Humana’s plans, as it has been since FDA approval. Humana's 2018 Medicare cost-sharing structure for Herceptin changed under select Medicare Advantage plans in 4 markets and is now the same as [under] most other Medicare Advantage plans and original Medicare.”16

Asked if she’d heard about Humana’s action happening in other markets, Rugo said, “I haven’t heard of a reclassification to a non-preferred drug. I think that they’re doing that ahead of time in preparation for the biosimilar availability in the next year. I’m guessing that that will happen wholesale, that every regulatory group and mass insurer will change to say trastuzumab is what is preferred, and the type of trastuzumab doesn’t matter.”20

Humana did not respond to several requests for comment from *EBO™*, including a question regarding whether Herceptin’s move to a nonpreferred formulary tier occurred in anticipation of Ogivri’s availability. There has been considerable outcry...
over Humana’s move, since cancer patients do not yet have a substitute for Herceptin.

But once Ogivri arrives, making the biosimilar the preferred therapy would not be without precedent. Rugo said she has already seen this happen at the institution level with filgrastim (Granix), the treatment for neutropenia that has a biosimilar competitor, filgrastim-sndz (Zarzio). In August 2016, CVS Health, the nation’s second-largest pharmacy benefit manager, announced it was dropping the mainstream insulin Lantus, a top seller for Sanofi, from its formulary in favor of Eli Lilly’s biosimilar, Basaglar.11

Having more approved biosimilars in the US market could be a game-changer in the marketplace, as it could be the best way to drive down the cost of biologic medications that have been on the market for years. The cost savings of treating people on far less costly biosimilars, even counting just newly diagnosed patients, were estimated to be an anticipated $250 billion by 2024 by Express Scripts in a 2013 report.20

The question remains: Will patients take advantage of these cost savings? “The FDA continues to grow the number of biosimilar approvals, helping to promote competition that can lower healthcare costs. This is especially important when it comes to diseases like cancer, that have a high cost burden for patients,” Gottlieb said. “We’re committed to taking new policy steps to advance our biosimilar pathway and promote more competition for biological drugs.”

As the FDA continues to approve more biosimilars, physicians’ reported attitudes towards them change. InCrowd surveyed physicians across 5 subspecialties in which biosimetrics is significant: dermatology, endocrinology, gastroenterology, oncology, and rheumatology. In November 2016, 84% of those surveyed said that they expect to prescribe, assume they will prescribe, or look forward to prescribing more biosimilars in the coming 3 years, up from 70% in February 2016.21 However, only 17% in November 2016 said they would allow pharmacy-level substitution of these drugs for their patients, versus 28% in February 2016.22 They continue to weigh more factors into their choice of potentially prescribing biosimilars at all.

“I think once the drugs are available, there’s going to be a big need for education and understanding of where these drugs should be and how comfortable people feel with them,” Rugo said, discussing biosimilars beyond cancer care. “But right now, I think in the United States because we can’t use them yet, the main interest has been in supportive care and in rheumatologic disease.”

Good Timing for Mylan

Ogivri was approved by the FDA based on a review of evidence including structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrate the molecule’s biosimilarity to Herceptin.

However, the news of Ogivri’s approval could not have come at a better time for manufacturer Mylan, which had been criticized over pricing strategy for its emergency allergy product, the EpiPen, and more recently, alleged drug price-fixing.

Mylan President Rajiv Malik, the company’s second-ranked executive, was accused of taking part in a “vast and sinister price-fixing conspiracy among global makers of generic pills that kept prices of the medications artificially high,” nearly every US state claimed in a new lawsuit.24

This 243-page complaint states that Mylan, along with 17 other generic drug makers, conspired to fix prices of certain critical treatments for patients suffering from conditions such as diabetes, hypertension, high blood pressure, and rheumatoid arthritis, according to new allegations by the top law enforcement officials in 46 states.25

The complaint comes less than a year after Mylan was at the center of a firestorm over the soaring prices of the EpiPen, which is used as a rescue product for those with severe allergies who experience anaphylaxis. The price of the product, which costs Mylan about $30 to produce, increased more than 50% when it rose from $103.50 in 2009 to more than $608.61 in 2016.26

Rugo, for her part, said the price points will matter, because if payers and institutions see the potential for large savings, “then they will want us to switch over to the biosimilars, which I am very happy to do. I think these are agents which are biosimilar, so I don’t have a problem switching over. And I don’t have a problem a switching a patient, either. “It’s going to be an interesting time to see what happens,” she said. •

REFERENCES


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