SPECIAL ISSUE: IMMUNO-ONCOLOGY

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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,[1] 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 RORγ 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."[2]

Wes Hall, far left, with staff of the Florida Cancer Specialists at the Thanksgiving Dinner event in November.
Photo Courtesy of Florida Cancer Specialists & Research Institute

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INTERVIEW

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

Mary Caffrey

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]).[1,2] 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.[3]

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BIOSIMILARS

Recent Approval of Trastuzumab Biosimilar, Ogivri, Has Implications for Patients and Industry

Samantha DiGrande

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),[1] the FDA approved Mylan and Biocon's trastuzumab biosimilar MYL-14010 in December 2017,[2] referenced on the drug trastuzumab (Herceptin).

Mylan's biosimilar, which will be marketed in the United States as Ogivri,[2] 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.[3] A report in *FiercePharma* noted that Herceptin has 90% market share for HER2-positive breast cancer, which affects 15% to 20% of patients,[4] and various sources listed the drug's price at $64,000 to $70,000 a year in 2016.[5,6]

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ADT = androgen-deprivation therapy; PSA = prostate-specific antigen.
*Estimated prevalence based on a dynamic progression model.

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MOLECULAR TESTING
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Use of biomarkers will become more important as the cost of immunotherapy increases. Among recent developments, FDA has approved Foundation Medicine's test for variants in 324 genes known to drive cancer.

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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 companion 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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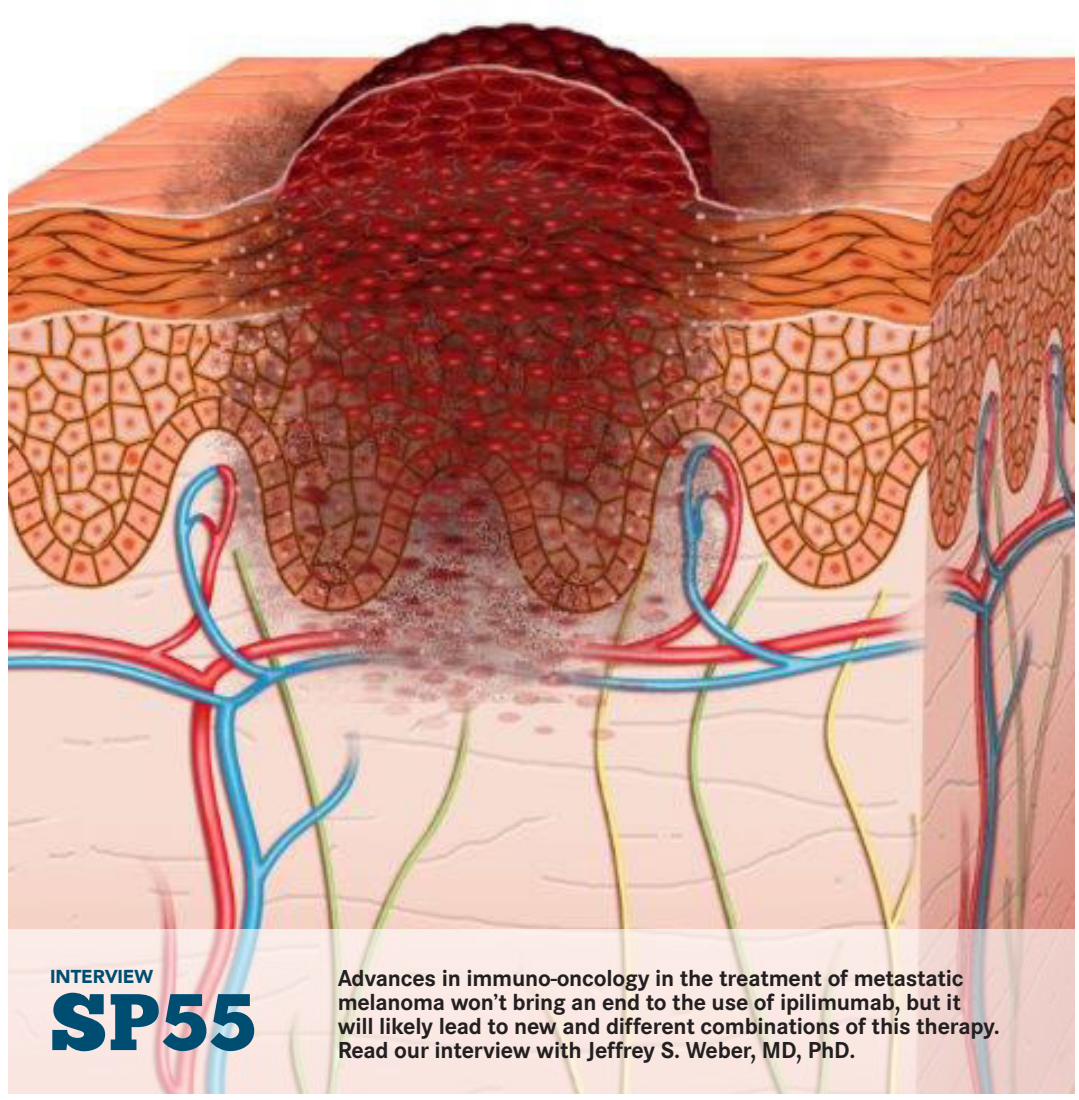

INTERVIEW
SP55
Advances in immuno-oncology in the treatment of metastatic melanoma won't bring an end to the use of ipilimumab, but it will likely lead to new and different combinations of this therapy. Read our interview with Jeffrey S. Weber, MD, PhD.

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FROM THE EDITOR-IN-CHIEF

Future Shock: Embracing Disruption in the Immunotherapy Revolution


ALVARNAS

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.[1] 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:

"... (A)n 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."[2]

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.[3]

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.[4] 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 Oncology*™ (*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 conveys 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 equitability of these life-changing care technologies. ◆

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Joseph Alvarnas, MD
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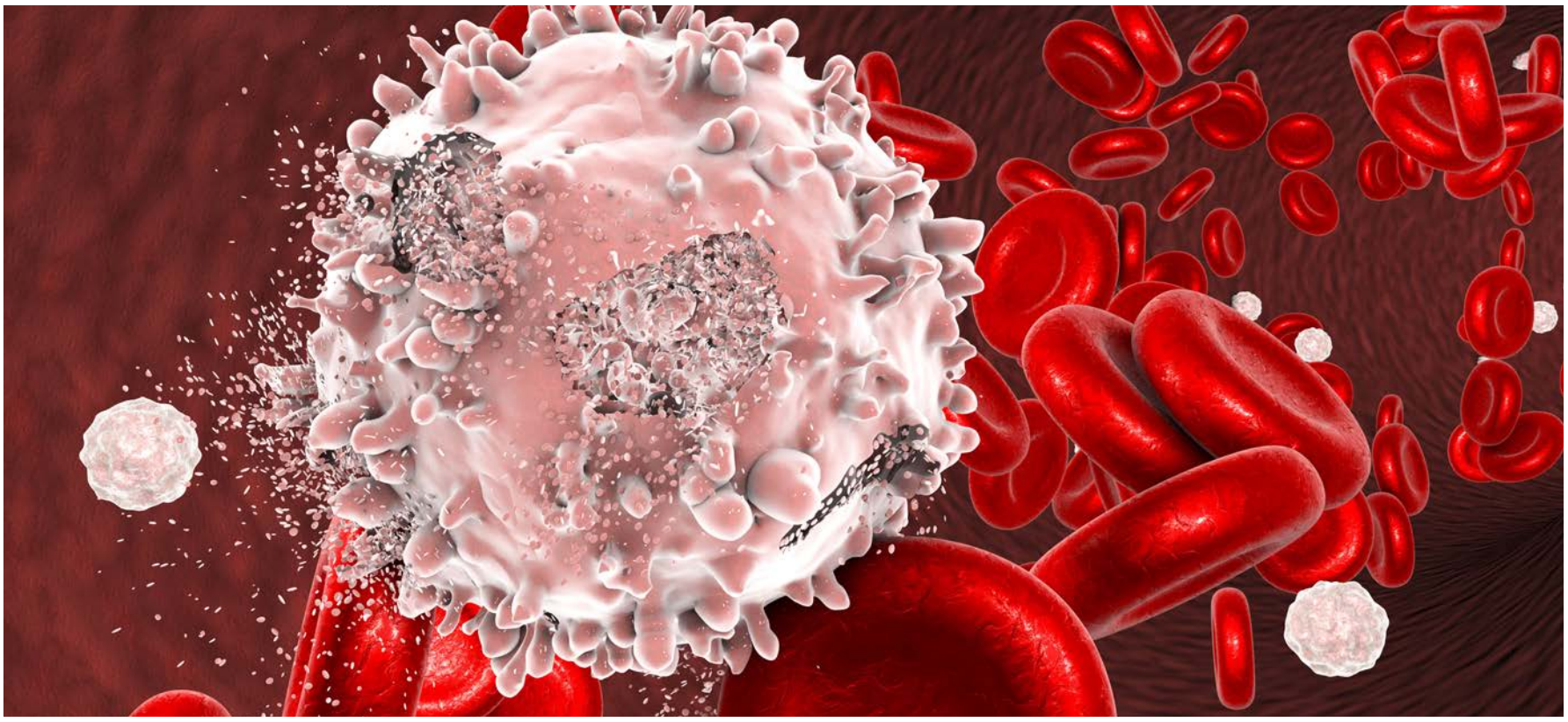
EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

PAYER COVERAGE

With Approval of CAR T-Cell Therapy Comes the Next Challenge: Payer Coverage

Mary Caffrey



A leukemia cancer cell in the blood stream. Chimeric antigen receptor (CAR) T-cell therapy is poised to revolutionize treatment of certain treatment resistant leukemias and lymphomas, but at a high cost.

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.[3] 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 *Health Affairs* as *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.[6]

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."[5]

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

system," with Kymriah as the first therapy subject to the agreement.[8] In short, CMS won't pay for those patients who fail to respond in the first 28 days of treatment.[6] 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 in 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

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 impatient 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 report progress in obtaining commercial coverage; Gilead reported that commercial payers would likely account for between 50% and 60% of Yescarta'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. ◆

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

AJMC Staff

A LONG-TERM FOLLOW-UP 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 medial 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. ◆

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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, BSPharm

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.

Introduction

LUNG CANCER IS THE leading cause of death from cancer worldwide.[1] In the United States, more than 225,500 new lung cancer cases and 155,870 lung cancer–related deaths were expected in 2017, making lung cancer the second most prevalent cancer among both men and women.[2] Non–small-cell lung cancer (NSCLC) is the most common form of lung cancer, representing approximately 85% of all cases.[3] NSCLC is characterized by a number of genomic alterations (mutations, rearrangements, and amplifications), and these alterations are responsible for initiating and maintaining tumor growth through constitutive activation of oncogenic signaling pathways.[4] Oncogenic genomic alterations (hereafter referred to as driver mutations) in lung cancer have been identified in genes encoding *EGFR, ALK, ROS1, BRAF, MET, RET*, and *HER2*, among others.[5]

The development of therapies targeting known driver mutations has permanently altered the treatment landscape of NSCLC.[6] The use of targeted therapies in patients harboring specific genomic alterations for which a specific therapy was developed is associated with improved treatment response and survival.[6] Indeed, in recent studies, patients with NSCLC who received targeted therapy were shown to have a higher overall response rate—both in first- and second-line settings[7]—as well as prolonged progression-free[7] and overall survival compared with patients not receiving targeted therapy.[7,8] Currently, FDA-approved targeted therapies for NSCLC are available targeting *EGFR, ALK, ROS1*, and *BRAF*.[6,9-11] Other therapies are in development for targets such as *MET*, *HER2*, and *RET*.[12-14]

Targeted therapies first approved for other tumor types have also demonstrated clinical benefit in alterations existent in NSCLC. For example, the combination of dabrafenib (Tafinlar) and trametinib (Mekinist) was initially approved for *BRAF V600E* mutations in metastatic melanoma but now is also approved for *BRAF V600E* mutations in NSCLC.[10,11,15] *BRAF* mutations (primarily *V600E*) are present in approximately half of all cases of metastatic melanoma[16,17] but in just 1% to 4% of patients with NSCLC, with *V600E* being the most common variant.[7,18] Similar to other NSCLC subtypes, patients with *BRAF*-positive NSCLC receiving targeted therapy experience improved clinical outcomes as demonstrated by the interim results of a phase II trial.[19,20] Based on the results of this ongoing trial, the dabrafenib/trametinib combination received breakthrough therapy designation, followed by FDA approval for the treatment of *BRAF V600E*–positive NSCLC.[15] In addition, National Comprehensive Cancer Network (NCCN) guidelines for 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.[21]

KEY TO GENE NAMES

ALK	ALK receptor tyrosine kinase
BRAF	B-Raf proto-oncogene, serine/threonine kinase
EGFR	Epidermal growth factor receptor
HER2	erb-b2 receptor tyrosine kinase 2 (synonym: human epidermal growth factor receptor 2)
KRAS	KRAS proto-oncogene, GTPase
MET	MET proto-oncogene, receptor tyrosine kinase
RET	ret proto-oncogene
ROS1	ROS proto-oncogene 1, receptor tyrosine kinase

Source: Hugo Gene Nomenclature Committee.

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.[22] Accordingly, several clinical guidelines now endorse the use of broad molecular testing to identify actionable driver mutations for which targeted agents may be available.[21,23]

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 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.

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$.mp. or NSCLC.mp. or ((lung neoplasms/ or bronchial neoplasms/ or carcinoma, bronchogenic/) and (adenocarcinoma/ or adenocarcinoma, bronchioalveolar/ or carcinoma, large cell/ or carcinoma, squamous cell/)) or 2) lung or NSCLC or non–small-cell lung cancer.

TABLE 1. Guideline Recommendations for Molecular Testing of NSCLC

Guidelines	Summary of Recommendations
NCCN (2018)	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.
CAP/IASLC/AMP (2016)	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*.
ASCO (2014)	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.

AMP indicates Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IASLC, International Association for the Study of Lung Cancer; NCCN, National Comprehensive Cancer Network; NSCLC, 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 polices) 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,[24] 59 to objective 2,[25-82] 8 to objective 3,[25,30,31,83-87] and 11 to objective 4.[25,26,31,59,62,63,83,86,88-90] 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.

Clinical guidelines and consensus recommendations for molecular tests in NSCLC

The 2016 draft guidelines from CAP/IASLC/AMP support *BRAF* testing in NSCLC (**Table 1**).[91,92] 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.[91,92] 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.[21]

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*.[93]

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.[24]

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[a] – Test Description

				Detection of Classes of Genomic Alterations[c]			
Categories	**Examples of Test Names**	**Provider/ Organization**	**Covered Genes of Interest[b]**	**Point Muation/ Base Substitution–SNP**	**Insertion and Deletions (indels)**	**Rearrangements/ Fusions**	**CNAs[d]**
Large central/ national laboratories	Lung Cancer Comprehensive Mutation and Translocation Panel by NGS	ARUP Laboratories	*BRAF, ALK, EGFR, HER2, KRAS, RET,* and *ROS1*	✓	✓	✓	
	OncoVantage	Quest Diagnostics	*BRAF, ALK, EGFR, HER2, KRAS, MET, and RET*	✓		*	
	IntelliGEN	LabCorp	*BRAF, ALK, EGFR, HER2, KRAS, MET,* and *RET*	✓		*	
Molecular diagnostics specialty companies	FoundationOne	Foundation Medicine	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*[e]	✓	✓	✓	✓
	Guardant 360	Guardant Health	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓	✓	✓	✓
	OncoGXLung	Rosetta Genomics	*BRAF, ALK, EGFR, KRAS,* and *ROS1*	✓	✓	✓	
	PCR - RosettaGX	Rosetta Genomics	*BRAF, EGFR, and KRAS*	✓			
	Lung Molecular Profile	Genoptix/Novartis	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓		*	
	GeneStrat	Biodesix	*BRAF, ALK, EGFR,* and *KRAS*	✓		*	
	OncoDEEP	OncoShare	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓	✓	✓	✓
	Lung Cancer NGS Panel - M LUNG NGS	Molecular Pathology Laboratory Network, Inc	*BRAF, ALK, EGFR, and KRAS*	✓		*	
	GeneTrails NSCLC Genotyping Panel	Knight Diagnostic Laboratories	*BRAF, EGFR, HER2,* and *KRAS*	✓			
	OncoPlexDx - Protein Expression Panel and Gene Mutation Panel	NantOmics	*BRAF, ALK, EGFR, HER2, KRAS, MET,* and *RET*	✓		*	
	MI Profile X	Caris Molecular Intelligence	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓	✓	*	✓
	OnkoMatch	GenPath	*BRAF, EGFR,* and *KRAS*	✓			
	SmartGenomics	PathGroup		✓			
	The Paradigm Center Diagnostic (PcDx) Panel	Paradigm	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓	✓	✓	
Academic laboratories	UW-OncoPlex - Cancer Gene Panel	University of Washington - Laboratory Medicine	*BRAF, ALK, EGFR, HER2, KRAS, MET, RET,* and *ROS1*	✓	✓	✓	✓
	MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)[f]	Memorial Sloan Kettering (MSK) Cancer Center		✓	✓	✓	✓

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

[a]Includes only tests available in the United States. [b]Only genes explicitly specified in websites are reported. More genes may be covered by the tests. [c]Only classes explicitly specified in websites are reported. Types of genomic alterations were not identified based on genes detected by the tests. [d]Ability to detect copy number alteration, copy number variation, or DNA amplifications. [e]Additional genes included in assay; a current list is available at foundationmedicine.com/genomic-testing/foundation-one. [f]MSK-IMPACT authorized to identify mutations in 468 genes, refer to MSK website for further details: mskcc.org/msk-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 4 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. Anecdotal 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[25] found that overall 81% of newly diagnosed patients with stage IIIb/IV NSCLC received testing for *EGFR* prior to first-line therapy; this percentage was lower among patients treated by US and European oncologists (77%).[94]

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 methods.[32,43,70,73-76,79,80,95,96] 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.[96] 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.[33-35,37,42,44,45,51,53,67,77-79,97-100]

Although liquid biopsy has been validated for *EGFR* testing,[101] 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 turnaround time on clinical outcomes were identified. However, it is obvious that assessing 50 genes at once will be faster than analyzing multiple genes in sequence, as is common in many laboratories.

Update

As of December 2017, other approved NGS tests included Oncomine Dx as well as the broader FoundationOne CDx (F1CDx) and Memorial Sloan Kettering Cancer Center's Integrated Mutation

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

		Sample Requirements			
Categories	**Examples of Test Names**	**FFPE Block or Tissue**	**Fine Needle Biopsy**	**Blood/Liquid Biopsy Sample**	**Purified DNA**
Large central/ national laboratories	Lung Cancer Comprehensive Mutation and Translocation Panel by NGS	Resections: 8 unstained 5-micron slides (>5 slides) Small biopsies: 15 unstained 5-micron slides (>10 slides)			
	OncoVantage	✓		2 ml whole blood	10 ul extracted DNA
	IntelliGEN	Five unstained slides and one matching H&E stained slide cut at 10 µM	5 ml to 10 ml fine needle aspirate		*
Molecular diagnostics specialty companies	FoundationOne	≥40 µm tissue, of which a minimum of 20% is of malignant origin, on 8 to 10 unstained slides or in an FFPE block	✓		
	Guardant 360			2 vials of blood	
	OncoGXLung	≥2.5 mm^2			
	PCR - RosettaGX				
	Lung Molecular Profile	2 FFPE block containing non-necrotic tumor tissue, plus 1 H&E slide cut at 4-5 microns or biopsy or 12 unstained slides at 10 µm thickness			
	GeneStrat			✓	
	OncoDEEP		✓		
	Lung Cancer NGS Panel - M LUNG NGS	3-5 slides at 5 micron minimum			
	GeneTrails NSCLC Genotyping Panel	✓	✓		20 ng DNA
	OncoPlexDx - Protein Expression Panel and Gene Mutation Panel	One 5 µm H&E section and 2-3 10 µm sections			
	MI Profile X				
	OnkoMatch				
	SmartGenomics				
	The Paradigm Center Diagnostic (PcDx) Panel	Six to ten 10 µm thick freshly cut curls along with H&E stained section of same block - 75 mm3 (5 mm x 5 mm x 3 mm)	4 to 6 needle biopsies		
Academic laboratories	UW-OncoPlex - Cancer Gene Panel	1 slide at 4-micron thickness stained with H&E and 10 unstained, non-baked slides at 10-micron thickness (≥5 unstained slides)	1 to 2 ml	6 ml blood	≥5 ug
	MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)[f]				

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.

[a]Includes only tests available in the US

Profiling 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.[102] 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.[103-105] 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.[103,104]

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,[25,106] the main reasons (beside 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.[94] 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.[106]

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."[107] 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[a] – Test Performance

			Specificity			Technical Performance		
Categories	**Examples of Test Names**	**Depth/ Coverage**	**Lung Specific**	**Solid Tumor Specific**	**Turnaround Time**	**Sensitivity**	**Specificity**	**Allele Burden Cut-Off**
Large central/ national laboratories	Lung Cancer Comprehensive Mutation and Translocation Panel by NGS		✓		12-14 days			5% mutant alleles
	OncoVantage™			✓	14 days			5% mutation
	IntelliGEN			✓	14-21 days			Detect a mutation present at 5% of background wild-type DNA
	FoundationOne	>500x		✓	14 days	≥90% (rearrangements) to >99% (base substitutions)	>99%	
	Guardant 360			✓	14 days		99.9999%	
Molecular diagnostics specialty companies	OncoGXLung		✓		7-10 days			
	PCR - RosettaGX		✓		1-4 days			
	Lung Molecular Profile		✓		12 days			
	GeneStrat		✓		3 days			
	OncoDEEP	1000x		✓	7 days	>99% (indel)		
	Lung Cancer NGS Panel - M LUNG NGS		✓		7-10 days			
	GeneTrails NSCLC Genotyping Panel		✓		10-14 days			≤10% mutant allele
	OncoPlexDx - Protein Expression Panel and Gene Mutation Panel			✓				
	MI Profile X			✓				
	OnkoMatch			✓				
	SmartGenomics	1000x avg		✓	7-10 days			
	The Paradigm Center Diagnostic (PcDx) Panel	5000x depth of coverage		✓	4-5 days			
Academic laboratories	UW-OncoPlex - Cancer Gene Panel			✓	4-6 weeks			
	MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)[f]			✓				

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

[a]Includes only tests available in the US

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.[61]

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.[106] 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.[109] 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."[32] 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*. ◆

For References, see EAppendix at ajmc.com/journals/evidence-based-oncology/2018/february-2018

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TABLE 5. A Selection of Medical Policies

		Considered As Medically Necessary								
Examples of Test Names	Approximate Number of Covered Lives	Panel Testing	*BRAF*	*ALK*	*EGFR*	*HER2 (ERBB2)*	*KRAS*	*MET*	*RET*	*ROS1*
Health Net, Inc.	10 million	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anthem-BlueCross BlueShield	38.6 million		✓							
Aetna[a]	22.99 million	✓		✓	✓		✓			✓
United Healthcare	70 million	✓		✓	✓	✓			✓	
Excellus[b]	1.5 million			✓	✓					
YourCare[b]	0.055 million			✓	✓					
Univera[b]	1.5 million			✓	✓					
Blue Cross Blue Shield of Massachusetts	2.8 million			✓	✓					✓
Blue Cross of Idaho	0.8 million				✓[c,d]					
Blue Cross Blue Shield of Mississippi	0.185 million			✓[c]	✓[c,d]					
Blue Cross Blue Shield of Alabama	3 million			✓[c]	✓[c,d]					
Blue Cross Blue Shield of California	4 million			✓[c]	✓[c,d]					
Protocol	-			✓[c]	✓[c,d]					✓
Blue Cross Blue Shield of Georgia	3 million		✓							
Blue Cross Blue Shield of Kansas City	0.95 million			✓[c]	✓[c,d]					
CMS Local Coverage Determinations[e]	-	✓	✓	✓	✓	✓	✓	✓	✓	✓

CGP indicates comprehensive genomic profiling; LDC, local coverage determination; NSCLC, non–small cell lung cancer
[a]There is some contradictory information in the Aetna policies. *BRAF* V600 mutation analysis is reported as experimental and investigational for NSCLC. In contrast, "targeted solid organ genomic sequencing panel (5-50 genes) for NSCLC" is reported as medically necessary. [b]Coverage for Medicare product members. [c]Considered as medically necessary only in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded. [d]Analysis for *EGFR* mutations within exons 18-24 is considered investigational. [e]CGP is covered only when the following conditions are met: a) Patient has been diagnosed with advanced (Stage IIIB or IV) NSCLC; and, b) Patient is a lifetime nonsmoker or former light smoker with ≤15 pack year history of smoking; and, c) Patient previously tested negative for *EGFR* mutations, *ALK* rearrangements, and *ROS1* rearrangements through non CGP methods; and, d) Testing is performed by a lab that satisfies the MolDX program contractor's published AV criteria. The LCDs include the following states: Alaska, Arizona, California, Connecticut, Hawaii, Idaho, Illinois, Kentucky, Maine, Massachusetts, Minnesota, Montana, New York, Nevada, New Hampshire, North Dakota, Ohio, Oregon, Rhode Island, South Carolina, South Dakota, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin, and Wyoming.

Cancer Gene Profiling Test Can Open Doors to New Targeted Therapies

Jaime Rosenberg

ON NOVEMBER 30, 2017, the FDA granted approval to Foundation Medicine's first-of-a-kind comprehensive companion diagnostic test for solid tumors, FoundationOne CDx.[1] While it gives patients the ability to be accurately matched with a targeted therapy, this test also opens doors to the development of new targeted therapies, explained Stuart Goldberg, MD, chief scientific officer, Cota, in an interview with *The American Journal of Managed Care®*.

The comprehensive genomic profiling test looks at genomic alterations in 324 genes known to drive cancer growth.[1] "This test is designed to try and find specific mutations, driver mutations, that we think may cause or accelerate the solid tumor cancers," explained Goldberg.

FoundationOne CDx marks a shift in precision medicine, in which a doctor can get a clearer picture of a patient's cancer and be being able to better direct them toward a clinical pathway. The test will identify patients who will benefit from targeted therapies; an estimated 1 in 3 patients across 5 common advanced cancers will likely be matched with 1 of the 17 on-label targeted therapies.[1]

"What you're trying to look for is: is there a gene that is altered or mutated, and is that gene so-called actionable? So, do we have a pill or targeted therapy to turn that gene off, and if that gene is what's causing that cancer to get angry, maybe by turning off that gene you can slow down the progression of the cancer or maybe even put the patient in remission," said Goldberg.

The best example of this can be seen in lung cancer. According to Goldberg, about 1 in 3 patients with lung cancer have mutations, and it's been shown that if they are "turned off," the cancer will slow down. The test also has potential benefits for patients with a less common type of cancer, because although the test will screen for all 7 known mutations for lung cancer, it will also test for 300 mutations for other cancers.

With this ability, the test will also allow doctors to refer patients for clinical trial participation if there is no available therapy. If it's discovered that a lot of patients have a certain mutation, there is a possibility that someone will start developing a drug for it, said Goldberg.

"So now when we get beyond the standard lung cancer, colon cancer, breast cancer—beyond the big ones—the fact that we can now take these rarer cancers, where we may not have had ideas of what to do, and do these genetic tests will help patients, hopefully dramatically," he said.

Until now, there has been difficulty getting insurance companies to cover these types of tests, with the argument that if there are 4 available targeted therapies, why not just test for those 4 genes? However, Goldberg argued that getting more information from the hundreds of tested genes will pave the way to being able to target more genes.

Providing relief for physicians and patients, CMS' joint approval of FoundationOne CDx means that Medicare will cover the test, which runs for about $3000 to $5000, according to Goldberg. ◆

REFERENCE

FDA approves Foundation Medicine's FoundationOne CDx, the first and only comprehensive genomic profiling test for all solid tumors incorporating multiple companion diagnostics [press release]. Cambridge, MA: Foundation Medicine; November 30, 2017. Investors.foundationmedicine.com/releasedetail.cfm?releaseid=1050380. Accessed January 9, 2018.

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 the APHINITY (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% Cl, 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 pro portion of IDFS events for patients with node-positive 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 to 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."[3]

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.[1] ◆

REFERENCES

1. FDA grants regular approval to pertuzumab for adjuvant treatment of HER2-positive breast cancer [press release]. Washington, DC: FDA; December 20, 2017. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm590005.htm. Accessed December 21, 2017.
2. Von Minckwitz G, Procter M, de Azambuia E, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(12):122-131. doi: 10.1056/NEJMoa1703643.
3. FDA approves Roche's Perjeta (pertuzumab) for adjuvant treatment of specific type of breast cancer [press release]. Basel, Switzerland: Roche; December 21, 2017. roche.com/media/store/releases/med-cor-2017-12-21b.htm. Accessed January 9, 2018.

#1 PRESCRIBED THERAPY IN FRONTLINE* AND PREVIOUSLY TREATED CLL[1†]

TAKE CONTROL OF CLL/SLL WITH YOUR FIRST STEP: IMBRUVICA® (ibrutinib)

Proven results across key efficacy endpoints: PFS and OS[2]

*Based on market share data from IMS from November 2016 to April 2017.
†Based on market share data from IMS from May 2014 to April 2017.

CLL
SLL

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)[2]
- CLL/SLL with 17p deletion[2]

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

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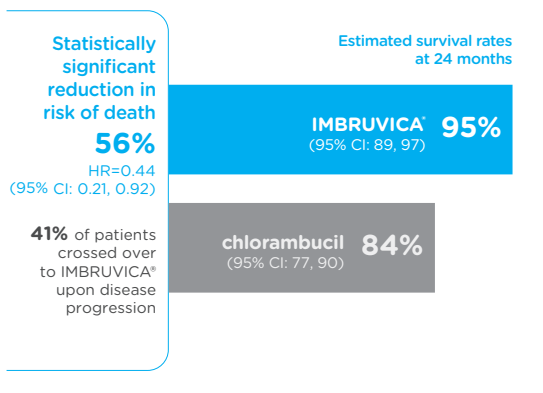
RESONATE™-2 FRONTLINE DATA

RESONATE™-2 was a multicenter, randomized 1:1, open-label, Phase 3 trial of IMBRUVICA® vs chlorambucil in frontline CLL/SLL patients ≥65 years (N=269)[2,3] Patients with 17p deletion were excluded[3]

EXTENDED OVERALL SURVIVAL[2]

SECONDARY ENDPOINT: OS IMBRUVICA® vs CHLORAMBUCIL

Reduced risk of death by more than half

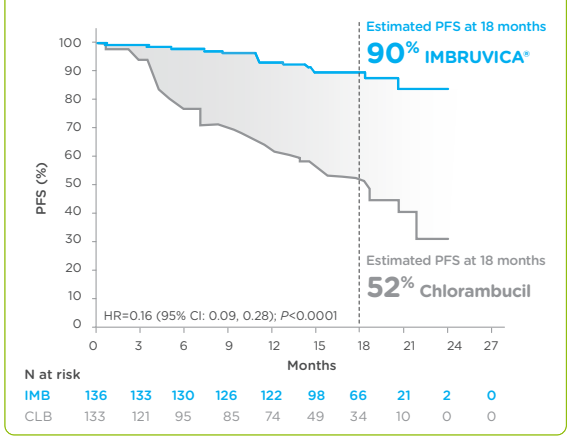


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

PROLONGED PROGRESSION-FREE SURVIVAL[2,3]

PRIMARY ENDPOINT: PFS IMBRUVICA® vs CHLORAMBUCIL

84% statistically significant reduction in risk of progression or death[2,3]



- Median follow-up was 18 months[3]
- With IMBRUVICA®, median PFS was not reached vs 18.9 months (95% CI: 14.1, 22.0) with chlorambucil[2]
- PFS and ORR (CR and PR) were assessed by an IRC according to the revised 2008 iwCLL criteria[3]

RESONATE™-2 Adverse Reactions ≥15%

- Diarrhea (42%)
- Musculoskeletal pain (36%)
- Cough (22%)
- Rash (21%)
- Bruising (19%)
- Peripheral edema (19%)
- Pyrexia (17%)
- Dry eye (17%)
- Arthralgia (16%)
- Skin infection (15%)

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 (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (39%), thrombocytopenia (16%), and pneumonia (10%).

Approximately 6% (CLL/SLL), 14% (MCL), 11% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4%-10% (CLL/SLL), 9% (MCL), and 9 % (WM [6%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%), muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%), and pneumonia (21%).

The most common Grade 3 or 4 adverse reactions (≥5%) reported 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 coadministration with strong CYP3A inducers.

CYP3A Inhibitors: Dose adjustment may be recommended.

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.

CI=confidence interval, CLL=chronic lymphocytic leukemia, HR=hazard ratio, IRC=Independent Review Committee, iwCLL=International Workshop on CLL, OS=overall survival, PFS=progression-free survival, SLL=small lymphocytic lymphoma.

References: 1. Data on file. Pharmacyclics LLC. **2.** IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC 2017. **3.** Burger JA, Tedeschi A, Barr PM, et al; for the RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.

To learn more, visit
IMBRUVICAHCP.com

imbruvica®
(ibrutinib) 140mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

Mantle Cell Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.2) in Full Prescribing Information]*.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion *[see Clinical Studies (14.2) in Full Prescribing Information]*.

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.3) in Full Prescribing Information]*.

Marginal Zone Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.4) in Full Prescribing Information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Chronic Graft versus Host Disease: IMBRUVICA is indicated for the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy *[see Clinical Studies (14.5) in Full Prescribing Information]*.

CONTRAINDICATIONS

None

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 *[see Clinical Studies (14) in Full Prescribing Information]*.

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 *[see Adverse Reactions]*. 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 *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

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. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with hematologic malignancies. 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 *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Cytopenias *[see Warnings and Precautions]*
- Atrial Fibrillation *[see Warnings and Precautions]*
- Hypertension *[see Warnings and Precautions]*
- Second Primary Malignancies *[see Warnings and Precautions]*
- Tumor Lysis Syndrome *[see Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial (Study 1104) that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with MCL (N=111)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	51	5
	Nausea	31	0
	Constipation	25	0
	Abdominal pain	24	5
	Vomiting	23	0
	Stomatitis	17	1
	Dyspepsia	11	0
Infections and infestations	Upper respiratory tract infection	34	0
	Urinary tract infection	14	3
	Pneumonia	14	7
	Skin infections	14	5
	Sinusitis	13	1
General disorders and administration site conditions	Fatigue	41	5
	Peripheral edema	35	3
	Pyrexia	18	1
	Asthenia	14	3
Skin and subcutaneous tissue disorders	Bruising	30	0
	Rash	25	3
	Petechiae	11	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	37	1
	Muscle spasms	14	0
	Arthralgia	11	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	27	4
	Cough	19	0
	Epistaxis	11	0
Metabolism and nutrition disorders	Decreased appetite	21	2
	Dehydration	12	4
Nervous system disorders	Dizziness	14	0
	Headache	13	0

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with MCL (N=111)

	Percent of Patients (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	57	17
Neutrophils Decreased	47	29
Hemoglobin Decreased	41	9

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: The data described below reflect exposure in one single-arm, open-label clinical trial (Study 1102) and three randomized controlled clinical trials (RESONATE, RESONATE-2, and HELIOS) in patients with CLL/SLL (n=1278 total and n=668 patients exposed to IMBRUVICA). Study 1102 included 51 patients with previously treated CLL/SLL, RESONATE included 391 randomized patients with previously treated CLL or SLL who received single agent IMBRUVICA or ofatumumab, RESONATE-2 included 269 randomized patients 65 years or older with treatment naïve-CLL or SLL who received single agent IMBRUVICA or chlorambucil, and HELIOS included 578 randomized patients with previously treated CLL or SLL who received IMBRUVICA in combination with bendamustine and rituximab or placebo in combination with bendamustine and rituximab.

The most commonly occurring adverse reactions in Studies 1102, RESONATE, RESONATE-2, and HELIOS in patients with CLL/SLL receiving IMBRUVICA (≥ 20%) were neutropenia, thrombocytopenia, anemia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia and hemorrhage. Four to 10 percent of patients receiving IMBRUVICA in Studies 1102, RESONATE, RESONATE-2, and HELIOS discontinued treatment due to adverse reactions. These included pneumonia, hemorrhage, atrial fibrillation, rash and neutropenia (1% each). Adverse reactions leading to dose reduction occurred in approximately 6% of patients.

Study 1102: Adverse reactions and laboratory abnormalities from the CLL/SLL trial (N=51) using single agent IMBRUVICA 420 mg daily in patients with previously treated CLL/SLL occurring at a rate of ≥ 10% with a median duration of treatment of 15.6 months are presented in Tables 3 and 4.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	59	4
	Constipation	22	2
	Nausea	20	2
	Stomatitis	20	0
	Vomiting	18	2
	Abdominal pain	14	0
	Dyspepsia	12	0
Infections and infestations	Upper respiratory tract infection	47	2
	Sinusitis	22	6
	Skin infection	16	6
	Pneumonia	12	10
	Urinary tract infection	12	2
General disorders and administration site conditions	Fatigue	33	6
	Pyrexia	24	2
	Peripheral edema	22	0
	Asthenia	14	6
	Chills	12	0
Skin and subcutaneous tissue disorders	Bruising	51	2
	Rash	25	0
	Petechiae	16	0
Respiratory, thoracic and mediastinal disorders	Cough	22	0
	Oropharyngeal pain	14	0
	Dyspnea	12	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	25	6
	Arthralgia	24	0
	Muscle spasms	18	2
Nervous system disorders	Dizziness	20	0
	Headache	18	2
Metabolism and nutrition disorders	Decreased appetite	16	2
Neoplasms benign, malignant, unspecified	Second malignancies*	12*	0
Vascular disorders	Hypertension	16	8

* One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CLL/SLL (N=51) in Study 1102

	Percent of Patients (N=51)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	69	12
Neutrophils Decreased	53	26
Hemoglobin Decreased	43	0

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

RESONATE: Adverse reactions and laboratory abnormalities described below in Tables 5 and 6 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

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

Body System Adverse Reaction	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	11	2
Pneumonia*	15	10	13	9
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Petechiae	14	0	1	0
Bruising*	12	0	1	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Injury, poisoning and procedural complications				
Contusion	11	0	3	0
Eye disorders				
Vision blurred	10	0	3	0

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.
* Includes multiple ADR terms

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

	IMBRUVICA (N=195)		Ofatumumab (N=191)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Neutrophils Decreased	51	23	57	26
Platelets Decreased	52	5	45	10
Hemoglobin Decreased	36	0	21	0

RESONATE-2: Adverse reactions described below in Table 7 reflect exposure to IMBRUVICA with a median duration of 17.4 months. The median exposure to chlorambucil was 7.1 months in RESONATE-2.

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

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea	42	4	17	0
Stomatitis*	14	1	4	1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	36	4	20	0
Arthralgia	16	1	7	1
Muscle spasms	11	0	5	0
Eye Disorders				
Dry eye	17	0	5	0
Lacrimation increased	13	0	6	0
Vision blurred	13	0	8	0
Visual acuity reduced	11	0	2	0
Skin and subcutaneous tissue disorders				
Rash*	21	4	12	2
Bruising*	19	0	7	0
Infections and infestations				
Skin infection*	15	2	3	1
Pneumonia*	14	8	7	4
Urinary tract infections	10	1	8	1

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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)

Body System Adverse Reaction	IMBRUVICA (N=135)		Chlorambucil (N=132)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough	22	0	15	0
General disorders and administration site conditions				
Peripheral edema	19	1	9	0
Pyrexia	17	0	14	2
Vascular Disorders				
Hypertension*	14	4	1	0
Nervous System Disorders				
Headache	12	1	10	2

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.
* Includes multiple ADR terms

HELIOS: Adverse reactions described below in Table 8 reflect exposure to IMBRUVICA + BR with a median duration of 14.7 months and exposure to placebo + BR with a median of 12.8 months in HELIOS in patients with previously treated CLL/SLL.

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

Body System Adverse Reaction	Ibrutinib + BR (N=287)		Placebo + BR (N=287)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders				
Neutropenia*	66	61	60	55
Thrombocytopenia*	34	16	26	16
Skin and subcutaneous tissue disorders				
Rash*	32	4	25	1
Bruising*	20	<1	8	<1
Gastrointestinal disorders				
Diarrhea	36	2	23	1
Abdominal Pain	12	1	8	<1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	29	2	20	0
Muscle spasms	12	<1	5	0
General disorders and administration site conditions				
Pyrexia	25	4	22	2
Vascular Disorders				
Hemorrhage*	19	2	9	1
Hypertension*	11	5	5	2
Infections and infestations				
Bronchitis	13	2	10	3
Skin infection*	10	3	6	2
Metabolism and nutrition disorders				
Hyperuricemia	10	2	6	0

The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.
* Includes multiple ADR terms
<1 used for frequency above 0 and below 0.5%

Atrial fibrillation of any grade occurred in 7% of patients treated with IMBRUVICA + BR and 2% of patients treated with placebo + BR. The frequency of Grade 3 and 4 atrial fibrillation was 3% in patients treated with IMBRUVICA + BR and 1% in patients treated with placebo +BR.

Waldenström's Macroglobulinemia and Marginal Zone Lymphoma: The data described below reflect exposure to IMBRUVICA in open-label clinical trials that included 63 patients with previously treated WM (Study 1118) and 63 patients with previously treated MZL (Study 1121).

The most commonly occurring adverse reactions in Studies 1118 and 1121 (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, fatigue, bruising, hemorrhage, anemia, rash, musculoskeletal pain, and nausea.

Nine percent of patients receiving IMBRUVICA across Studies 1118 and 1121 discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 10% of patients.

Study 1118: Adverse reactions and laboratory abnormalities described below in Tables 9 and 10 reflect exposure to IMBRUVICA with a median duration of 11.7 months in Study 1118.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	37	0
	Nausea	21	0
	Stomatitis*	16	0
	Gastroesophageal reflux disease	13	0
Skin and subcutaneous tissue disorders	Rash*	22	0
	Bruising*	16	0
	Pruritus	11	0
General disorders and administrative site conditions	Fatigue	21	0
Musculoskeletal and connective tissue disorders	Muscle spasms	21	0
	Arthropathy	13	0

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 (N=63) (continued)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection Sinusitis Pneumonia* Skin infection*	19 19 14 14	0 0 6 2
Respiratory, thoracic and mediastinal disorders	Epistaxis Cough	19 13	0 0
Nervous system disorders	Dizziness Headache	14 13	0 0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	Skin cancer*	11	0

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

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

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	43	13
Neutrophils Decreased	44	19
Hemoglobin Decreased	13	8

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)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea Nausea Dyspepsia Stomatitis* Abdominal pain Constipation Abdominal pain Upper Vomiting	43 25 19 17 16 14 13 11	5 0 0 2 2 0 0 2
General disorders and administrative site conditions	Fatigue Peripheral edema Pyrexia	44 24 17	6 2 2
Skin and subcutaneous tissue disorders	Bruising * Rash* Pruritus	41 29 14	0 5 0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain* Arthralgia Muscle spasms	40 24 19	3 2 3
Infections and infestations	Upper respiratory tract infection Sinusitis* Bronchitis Pneumonia*	21 19 11 11	0 0 0 10
Metabolism and nutrition disorders	Decreased appetite Hyperuricemia Hypoalbuminemia Hypokalemia	16 16 14 13	2 0 0 0
Vascular Disorders	Hemorrhage* Hypertension*	30 14	0 5
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	22 21	2 2
Nervous system disorders	Dizziness Headache	19 13	0 0
Psychiatric disorders	Anxiety	16	2

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

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

	Percent of Patients (N=63)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	49	6
Hemoglobin Decreased	43	13
Neutrophils Decreased	22	13

Chronic Graft versus Host Disease: The data described below reflect exposure to IMBRUVICA in an open-label clinical trial (Study 1129) 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 trial discontinued treatment 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% of Patients with cGVHD (N=42)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions	Fatigue Pyrexia Edema peripheral	57 17 12	12 5 0
Skin and subcutaneous tissue disorders	Bruising* Rash*	40 12	0 0
Gastrointestinal disorders	Diarrhea Stomatitis* Nausea Constipation	36 29 26 12	10 2 0 0
Musculoskeletal and connective tissue disorders	Muscle spasms Musculoskeletal pain*	29 14	2 5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia* Upper respiratory tract infection Sepsis*	21 19 10	10 0 10

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4(%)
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	14 12	0 2
Metabolism and nutrition disorders	Hypokalemia	12	7

The system organ class and individual ADR preferred terms are sorted in descending frequency order.
* Includes multiple ADR terms.

Table 14: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with cGVHD (N=42)

	Percent of Patients (N=42)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	33	0
Neutrophils Decreased	10	10
Hemoglobin Decreased	24	2

Additional Important Adverse Reactions: *Diarrhea:* Diarrhea of any grade occurred at a rate of 43% (range, 36% to 59%) of patients treated with IMBRUVICA. Grade 2 diarrhea occurred in 9% (range, 3% to 14%) and Grade 3 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 627), 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 17% 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, 2% Grade 2). The median time to first onset was 85 days (range, 1 to 414 days). Of the patients with visual disturbance, 61% 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 *[see Warnings & Precautions]*
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), onychoclasis
- 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[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, and troleandomycin.

Examples[a] of moderate CYP3A inhibitors include: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYP3A.

Patients with B-cell Malignancies: *Posaconazole:* Reduce IMBRUVICA dose to 140 mg once daily during coadministration with posaconazole at doses of no more than 200 mg BID *[see Dosage and Administration (2.4) in Full Prescribing Information]*. Avoid the coadministration of IMBRUVICA with posaconazole at doses of greater than 200 mg BID.

Voriconazole: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any dose of voriconazole *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Other Strong Inhibitors: Avoid concomitant administration of IMBRUVICA with other strong CYP3A inhibitors. Alternatively, interrupt IMBRUVICA therapy during the duration of strong CYP3A inhibitors if the inhibitor will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Moderate Inhibitors: Reduce IMBRUVICA dose to 140 mg once daily during coadministration with any moderate CYP3A inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor patients taking concomitant strong or moderate CYP3A inhibitors more frequently for adverse reactions of IMBRUVICA.

Patients with Chronic Graft versus Host Disease: *Moderate CYP3A Inhibitor:* Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]* for patients coadministered IMBRUVICA with any moderate CYP3A inhibitor.

Strong CYP3A Inhibitors: Reduce IMBRUVICA dose to 280 mg once daily for patients coadministered IMBRUVICA with

- posaconazole immediate-release tablet 200 mg BID or
- posaconazole delayed-release tablet 300 mg QD or
- voriconazole any dose

Modify the dose based on adverse reactions *[see Dosage and Administration (2.3) in Full Prescribing Information]*

Avoid concomitant administration of IMBRUVICA with posaconazole at higher doses and other strong CYP3A inhibitors. If these CYP3A inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA therapy during the duration of the inhibitor *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Effect of CYP3A Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYP3A inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYP3A inducers *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort[b].

[a] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

[b] The induction potency of St. John's wort may vary widely based on preparation.

USE IN SPECIFIC POPULATIONS

Pregnancy: *Risk Summary:* IMBRUVICA, a kinase inhibitor, can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-20 times the clinical doses of 420-560 mg daily produced embryofetal toxicity including structural abnormalities *(see Animal Data)*. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

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All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% 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 560 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 and 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 (2.6) 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].*

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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.


WEBER

"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 =.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, .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. ◆

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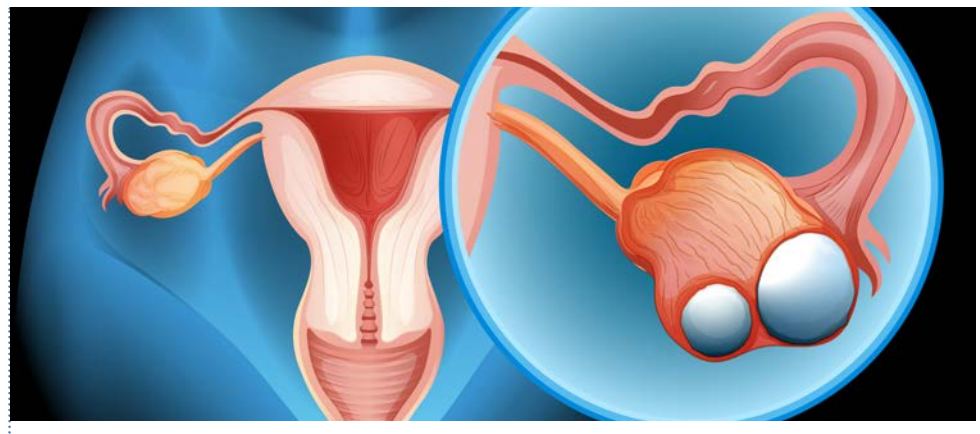
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Increased CD8+ TIL Counts Linked to Prolonged Survival in Patients With Certain Ovarian Cancers

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 (MOC), and low-grade serous OC (LGSOC). 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 LGSOC (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 germline *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 CCOC 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. ◆

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

Jaime Rosenberg

PREDIAGNOSIS 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 systematic 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 2470 patients from the Colorectal Cancer: Sarcopenia, Cancer, and Near-term Survival (C SCANS) 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 NRL 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 was 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, 1.10-1.67) 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 3 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." ◆

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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 *Journal of Clinical Oncology*.

Researchers reviewed claims from 2014 to 2015 from a large, proprietary, integrated database that included Medicare and commercial insurance enrollees for 38 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." ◆

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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 FROM COVER

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,[3] 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 abdominal area. 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.[4] 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.

"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."

—Wesley Hall, 3-time clinical trial participant

HALL

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.

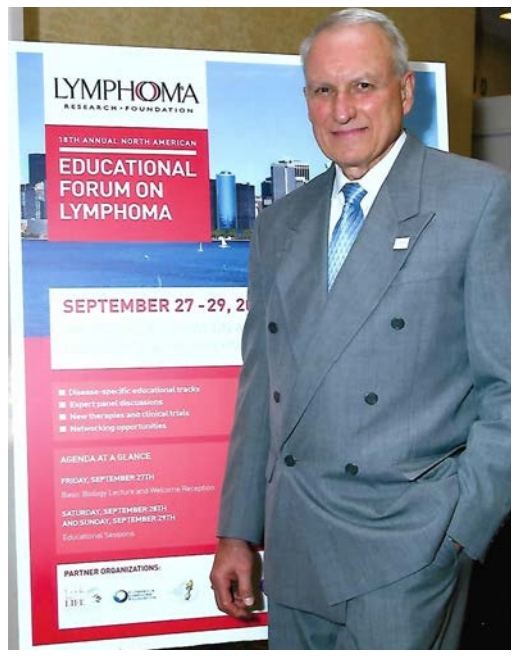
When he was diagnosed, Mesloh says, Farber told him there were 3 to 4 types of Hodgkin lymphoma and 22 to 24 types of non-Hodgkin lymphoma. Now, "to date, we know categorically, there are 80-plus types of non-Hodgkin's lymphoma," he says. The completion of the human genome project and other technological 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 "chokes 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 folinic acid and oxaliplatin (FOLFOX) and tivantinib, under the care of Sarasota-based researcher Manish Patel, MD.[5] "That worked for 2-and-a-half years," Hall says. (The



Robert Mesloh, diagnosed 20 years ago with follicular indolent non-Hodgkin lymphoma, has become an active ambassador for the Lymphoma Research Foundation. He was treated with a then-new rituxmab combination.

PHOTO COURTESY OF ROBERT MESLOH

trial results were reported this summer in *Cancer Investigation*.[6]) However, Hall says, "I had some pretty bad neuropathy in my hands and feet from the platinum-based drugs."

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 effects (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,[8] 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."[10]

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 November 2017, Jooma and Patel wanted to try "something my body hadn't already seen," as Hall puts it.
And so, as Christmas approached, Hall was preparing for a half-dozen trips from Dunedin to Sarasota in January, where he would put in 12-hour days having his blood drawn and getting other lab work done at the Sarasota research facility, to meet the standards needed for a clinical trial.

Each of those would be a long day for someone who doesn't have cancer, much less someone who does, but Hall doesn't mind. After more than 4 years, he feels a bond with both his community oncology team and his caregivers at the research center. Hall "never would have survived" at a large academic institution, he claims, and he raves, for instance, about the Thanksgiving dinner that Florida Cancer Specialists hosted for patients, complete with valet parking. "When I'm not sick, I go there and take them cookies and muffins," he says. "They're my family."

In his own family, he has experienced great loss. When Hall was in elementary school, his father died; in December 2016, Hall's middle son died of an illness caused by his work as a park ranger. Cancer has changed and shaped Hall's reality as well, but the disease has also led to positive changes. He's become a "gym rat," and he enjoys advocacy work with the Community Oncology Alliance. While he doesn't have grandchildren, he loves playing Santa for his neighbors' children.

"I have a real calmness about the whole thing," he says. "It is what it is. You just have to make the best of it."

"In the United States, only about 5% of our population who are diagnosed with a cancer will go on a clinical trial. That disappoints me."

—Robert Mesloh, 20-year cancer survivor; ambassador, Lymphoma Research Foundation

Too few patients take part in clinical trials

From his work with the LRF, Mesloh meets young researchers who are devoting their lives to finding cures for lymphoma and other cancers. "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 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 who are diagnosed with a cancer will go on to a clinical trial. That disappoints me," he says. To bring precision medicine to its potential, that percentage must grow, and it will take oncologists educating their patients and referring them outside their practices. "Too many people believe they are going to get a placebo," Mesloh says, even though that will not happen in most cases.

In lymphoma, "we are probably a decade away from being able to manage many of these [subtypes], based on the research that is in the [pipeline] now," Mesloh says. With the right funding, the field could see improvement on a trajectory that Mesloh calls "hockey-stick" exponential improvement, for the shape of the graph, instead of linear improvement.

For all he's learned since his diagnosis, some of the most important conversations at Mesloh's grant meetings come during the breaks, and they epitomize why he is there. Researchers who spend their days locked in a laboratory come talk to him, to quietly thank him for sharing what it's like to be a patient living with the disease. "They tell me, 'Bob, I need to be made aware of that issue. I don't hear enough of that,'" Mesloh relates.

Epilogue

Hall was feeling good during the latest trial as he headed into his first scan on February 6, 2018. But 2 days later, he learned the news "was not what I had hoped."

The lesion in his liver had spread, and he would have to come off the trial. Hall told *EBO*™ he remains at the top of the list for any new trial that covered his situation, and he wasted no time getting in to see Jooma the day after learning the news.

Given Hall's history with neuropathy from platinum-based chemotherapy, Jooma made plans to start a targeted therapy, to be followed by radiation.

Through it all, Hall's optimism came 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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CONTINUED FROM COVER

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

Mary Caffrey

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-naïve 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 education 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 pembro–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.[13,14])

"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.

"We'll need to look for all these other combinations," Weber said. "But it will be good for patients, because if the pembro–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

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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?"[15]

"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.[16]

"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-recognizing 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,[17] "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.[18]

As immunotherapy moves into the adjuvant population, the math becomes more challenging for payers and institutions if "the best you can do is

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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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CONTINUED FROM COVER

Recent Approval of Trastuzumab Biosimilar, Ogivri, Has Implications for Patients and Industry

Samantha DiGrande

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.[7]

But the situation could be changing. The *FiercePharma* report projected that Herceptin sales would fall to $3.98 billion by 2022.[4] Early in 2018, at least 1 national payer, Humana, has moved Herceptin to a less favorable formulary position in some markets[8]; 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 Biocon 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.[9]

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.[10]

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 whopping benefit, but it will cost a fortune."[13]

In the United States, this combination therapy was likely to cost about $115,000 for a year's worth of treatment in 2012.[12] By 2017, the cost of the same treatment rose to $158,000 with patients often staying on the regimen for more than a year, exacerbating costs further.[14]

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.[13]

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.[17]

"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."[18+]

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 Biocon 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.[16] While a precise arrival date of Ogivri is not known, a Barclays analyst projected it to be in 2019.[20]

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."[8]

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."

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 tbo-filgrastim (Granix), the treatment for neutropenia that has a biosimilar competitor, filgrastim-sndz (Zarxio). In August 2016, CVS Health, the nation's second-largest pharmacy benefit manager, announced it was dropping the mainstay insulin Lantus, a top seller for Sanofi, from its formulary in favor of Eli Lilly's biosimilar, Basaglar.[21]

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.[22]

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."[2]

As the FDA continues to approve more biosimilars, physicians' reported attitudes towards them change. *InCrowd* surveyed physicians across 5 subspecialties in which biologics prescribing 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.[23] However, only 17% in November 2016 said they would allow pharmacy-level substitution of these drugs for their patients, versus 28% in February 2016.[23] 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,[24] increased more than 500% 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. ◆

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