SPECIAL ISSUE: **ASCO MEETING RECAP**

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Evidence-Based ONCOLOGY™

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AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING | MAY 31-JUNE 4, 2019 | McCORMICK PLACE, CHICAGO, ILLINOIS

GOOD NEWS IN PANCREATIC CANCER?

Patients with germline genetic mutations did not see their pancreatic cancer worsen for an additional 3.6 months when treated with olaparib, according to results presented at the 2019 meeting of the American Society of Clinical Oncology (ASCO). But early results from the phase 3 POLO trial did not show a statistically significant difference in overall survival, **SP226**.

RISKS, REWARDS OF CAR T.

Chimeric antigen receptor (CAR) T-cell therapy can produce responses in patients with cancer who have exhausted other options, but cytokine release syndrome is a challenging reality. Several factors can predict the onset, according to 3 published studies discussed during a session, **SP234**.

DRUG PRICING DISCUSSION.

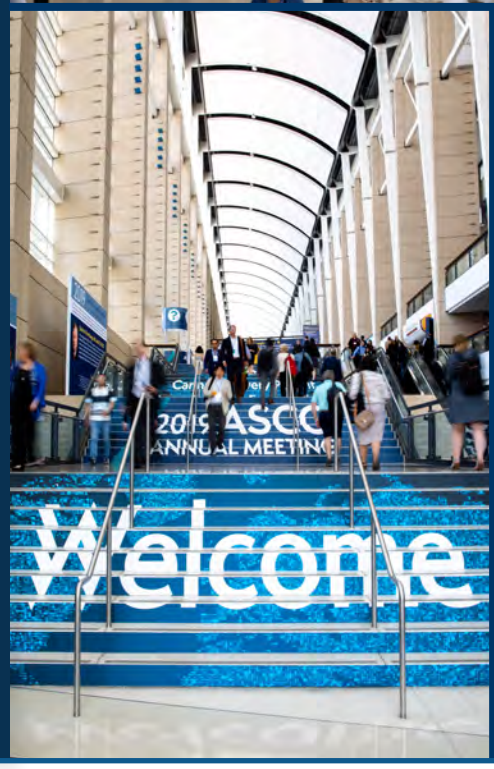
The prospect of tying US drug prices to an International Pricing Index and listing prices in direct-to-consumer advertising brought plenty of interest at a session during ASCO, **SP236**.

CANNABIS IN CANCER CARE?

"More research" was the bottom line at a session that discussed the use of cannabis for symptom management in cancer care, where panelists addressed the challenging legal landscape, which limits the ability to do meaningful research on the effects of medical cannabis, **SP238**.

COMBINATION THERAPY.

Abstracts presented at ASCO cover results involving nivolumab and ipilimumab combinations, **SP246-SP249**.



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TARGETING CANCER CELLS
INCLUDING CANCER STEM CELLS

Learn why rational approaches to cancer therapy should consider multiple cell types[1]

Two cancer cell subsets may drive tumor progression

At a high level, cancer cells can be categorized into two subsets:

- Mature, differentiated cancer cells
- Undifferentiated cancer stem cells (CSCs)

Differentiated cancer cells sustain and increase the volume of local tumors but lack the ability to self-renew. CSCs, however, possess the ability to originate tumors and metastasize.[2,3]

Therapies that target both subsets could help prevent tumor recurrence

While conventional chemotherapies may effectively target differentiated, proliferating cancer cells, CSCs can remain viable and reestablish tumors. The persistence of CSCs despite therapy could help explain why some tumors recur even after an initial reduction in size.[4] Therefore, targeting both CSCs and differentiated cancer cells may be a rational therapeutic strategy.[1]

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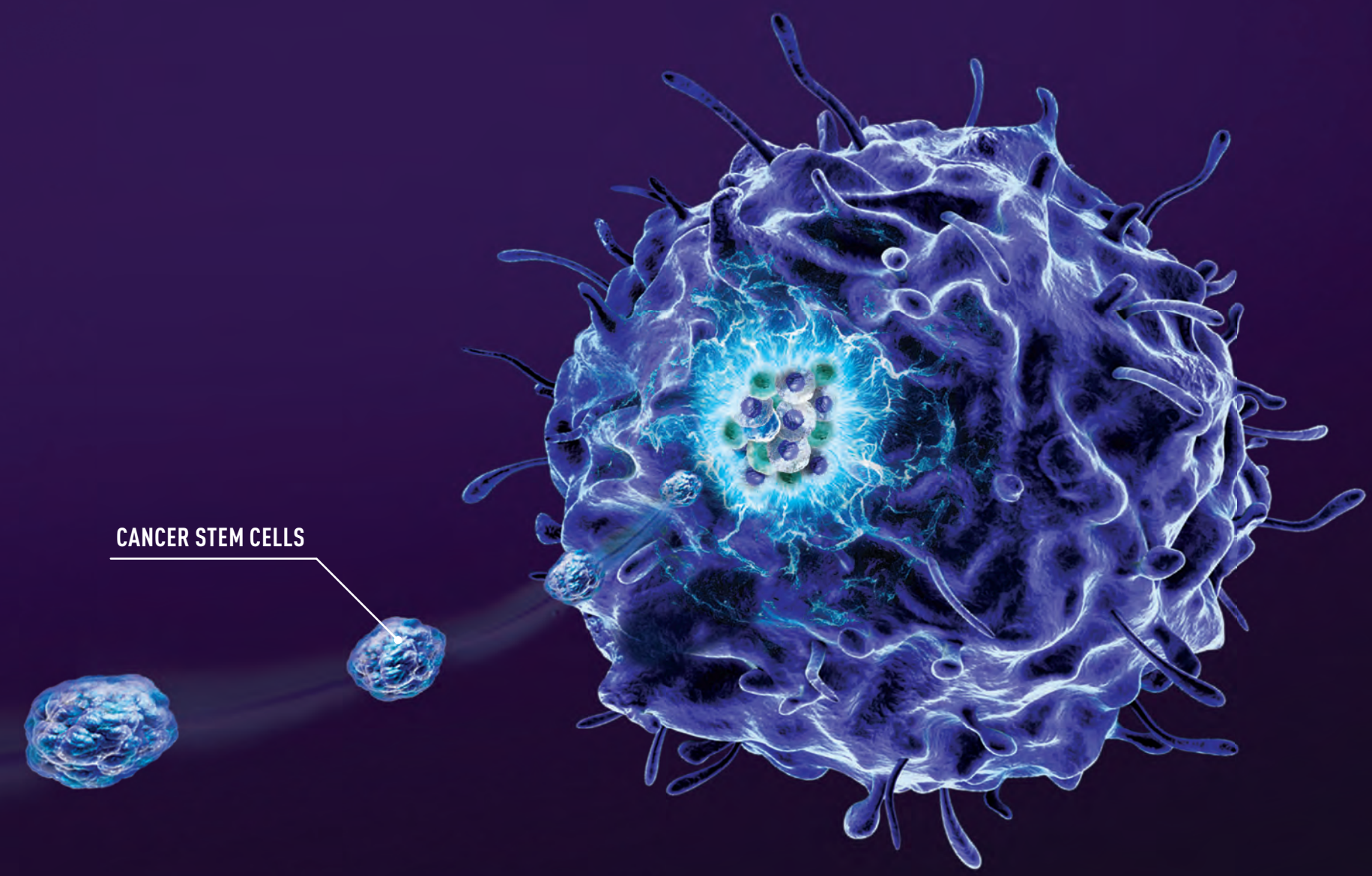

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SPECIAL ISSUE / ASCO Recap
JULY 2019
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Scenes above from the 2019 Annual Meeting of the American Society of Clinical Oncology, held May 31-June 4, 2019, at McCormick Place in Chicago, Illinois.

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Michael J. Birrer, MD, PhD, Director, O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham

Catherine M. Diefenbach, MD, Hematologist–Oncologist, NYU Langone Health

Roy S. Herbst, MD, PhD, Chief of Medical Oncology, Yale Cancer Center

Andrew H. Ko, MD, Colorectal and Gastrointestinal Cancer Specialist, University of California San Francisco

David Ortiz, Oncology Care Model Program Director, Montefiore Einstein Center for Cancer Care

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.

CLINICAL FINDINGS

Jaime Rosenberg, Mary Caffrey, Allison Inserro

Venetoclax–Obinutuzumab Demonstrates Efficacy Over Chlorambucil Combo in Untreated CLL

VENETOCLAX HAS PREVIOUSLY DEMONSTRATED efficacy in patients with chronic lymphocytic leukemia (CLL). Now, the results of a new study comparing the treatment plus obinutuzumab with the combination of chlorambucil and obinutuzumab have demonstrated that the venetoclax combination is associated with longer progression-free survival (PFS) among previously untreated patients with CLL and coexisting conditions.

At 24 months, PFS was 88.2% among patients receiving venetoclax–obinutuzumab compared with 64.1% among patients receiving chlorambucil–obinutuzumab. This survival benefit was observed regardless of *TP53* deletion, mutation, or both, in patients with unmutated *IGHV* and in other subgroups.

Results of the CLL14 trial, which were presented at the 2019 Annual Meeting of the American Society of Clinical Oncology in Chicago, Illinois, and published in the *New England Journal of Medicine*, led to the approval of the venetoclax combination for these patients in May.

The phase 3 trial was spread across 21 countries at 196 sites and enrolled 432 patients with CD20+ CLL who were randomized 1:1 to receive either venetoclax–obinutuzumab or chlorambucil–obinutuzumab for 12 cycles of treatment that lasted 28 days each.

Obinutuzumab was administered intravenously for 6 cycles starting with 100 mg on day 1 and 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 during cycles 2 through 6. Chlorambucil was administered orally at 0.5 mg/kg on days 1 and 15 of each cycle until completion of the 12 cycles. Venetoclax was initiated on day 22 of cycle 1, starting with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), and then was administered at 400 mg daily until completion of cycle 12.

At data cutoff, patients had discontinued therapy for a median of 17.1 months in the venetoclax–obinutuzumab group and 17.9 months in the chlorambucil–obinutuzumab group.

In the 3 months following completion, there were higher rates of patients in the venetoclax group who were negative for minimal residual disease in peripheral blood (75.5% vs 35.2%) and in bone marrow (56.9% vs 17.1%).

"Minimal residual disease negativity was consistently more common across all subgroups and was more sustainable with venetoclax–obinutuzumab than with chlorambucil–obinutuzumab," explained the researchers.

Patients treated with the venetoclax combination also had significantly higher rates of partial response (84.7% vs 71.3%) and complete response (49.5% vs 23.1%).

After a median follow-up of 28.1 months, there were 14 events of disease progression and 16 deaths among those receiving venetoclax–obinutuzumab and 69 events of disease progression and 8 deaths among those receiving chlorambucil–obinutuzumab.

Median overall survival (OS) was not reached in either treatment group, and during the complete observation period, OS did not differ significantly between the 2 groups.

There was at least 1 adverse event (AE) of any grade among 94.3% of patients receiving venetoclax–obinutuzumab and in 99.5% of patients receiving chlorambucil–obinutuzumab. These AEs resulted in treatment discontinuation among 16% of patients receiving the venetoclax combination and among 15.4% of patients receiving the chlorambucil combination.

The most common grade 3 or 4 AE was febrile neutropenia, and grade 3 or 4 infections were reported in 5.2% and 17.5% of patients, respectively, receiving the venetoclax combination, and in 3.7% and 15% of patients receiving the chlorambucil combination. During treatment, 5 fatal AEs occurred in the venetoclax–obinutuzumab group and 4 occurred in the chlorambucil–obinutuzumab group. Following treatment, 11 fatal AEs occurred in the venetoclax–obinutuzumab group and 4 occurred in the chlorambucil–obinutuzumab group. ◆

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More From TAILORx: Adding Clinical Risk to Genomic Testing Can Guide Therapy Choices in Breast Cancer

THE 21-GENE ASSAY, Oncotype DX, which a year ago was found to help many women with a common type of breast cancer avoid chemotherapy, may be best used alongside an assessment of tumor size and stage, according to investigators of the TAILORx trial.

But these new results published in the *New England Journal of Medicine*,[1] appear with an editorial that explores why they come a year after the original results. Precision medicine, the commentators say, is sometimes "messier" than the name suggests.[2]

Last year's practice-changing results were a headline of the 2018 meeting: chemotherapy with endocrine therapy after surgery offered no benefit for 70% of women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative, axillary node-negative breast cancer.

This time, Joseph A. Sparano, MD, of the Albert Einstein College of Medicine, and his coauthors used the same data to show that adding "clinical risk" to the equation—tumor size and histologic grade—offers extra prognostic value, "that, when added to the 21-gene recurrence score, could be used to identify premenopausal women who could benefit from more effective therapy."

However, the recommendations from these new results are drawn from other studies, not from the data.

"The promise of 'precision' medicine has collided with the rather messier world of using all available evidence to try to make educated guesses to improve patient outcomes. How could this be?"

—David J. Hunter, MBBS, and David L. Longo, MD

Reviewing TAILORx

The Oncotype DX assay provides a recurrence score of 0 to 100, with higher scores indicting worse prognosis. TAILORx enrolled 10,273 women with early breast cancer to learn more about the risks for patients with this type of cancer, specifically the risks for women with scores in the middle range, 11 to 25. Based on results from earlier trials, those with scores of 0 to 10 received endocrine therapy only; those with scores above 26 received endocrine therapy and chemotherapy. Those in the middle range were randomized to receive either chemotherapy and endocrine therapy or endocrine therapy alone. Patients were followed for 9 years.[3]

Results reported in June 2018 showed that although most women in this range did not need chemotherapy, some women would still benefit from it: those age 50 or younger with a recurrence score of 16 to 25.

Adding Clinical Risk

The investigators used a binary classification system from the MINDACT trial that divided patients into high or low risk based on tumor size and histologic grade. They report that the "integration of genomic and clinical information may provide a more accurate estimate of prognosis for individual patients than could be provided by either the genomic or clinical information alone."

Notably, the analysis found predictive information about recurrence, but not benefits of chemotherapy. Results showed:

- For women with recurrence scores of 11 to 25 who received endocrine therapy only, the hazard ratio comparing high clinical risk to low clinical risk was 2.73 (95% CI, 1.93-3.87).
- For women with recurrence scores of 11 to 25 who received chemotherapy and endocrine therapy, the hazard ratio for high versus low risk was 2.41 (95% CI, 1.66-3.48).
- For women with recurrence scores of 26 or higher, who all had both chemotherapy and endocrine therapy, the hazard ratio for high versus low risk was 3.17 (95% CI, 1.94-5.19).

Among women who were 50 years or younger who had endocrine therapy alone, the investigators wrote, "The estimated rate of distant recurrence at 9 years was less than 5%," with a low recurrence score, regardless of clinical risk.

The risk rose above 10% among younger women who had an intermediate recurrence score and high clinical risk.

Aromatase Inhibitor May Be an Option

So, what to do for these patients? Sparano et al noted that some of chemotherapy's ability to reduce death rates in younger women is attributed to its ability to induce menopause; while offering plenty of caution, they suggest that for some younger women, adding an aromatase inhibitor to tamoxifen may be in order.

They wrote, "Given the incremental benefits observed with ovarian suppression plus tamoxifen or an aromatase inhibitor, as compared with tamoxifen alone in premenopausal women, and the low percentage of premenopausal women who received ovarian suppression in TAILORx, it is possible that similar incremental benefits observed in younger women who received chemotherapy and had a recurrence score of 16 to 25 could be achieved with ovarian suppression and an aromatase inhibitor, as observed in other trials."

Unlike the clarity of last year's findings, the authors of the editorial said this time the TAILORx team must rely on interpretations. David J. Hunter, MBBS, and David L. Longo, MD, wrote that the investigators "speculate on the basis of previous studies that adding ovarian suppression and an aromatase inhibitor might give a reduction in risk equivalent to that observed using adjuvant chemotherapy."

"The promise of 'precision' medicine has collided with the rather messier world of using all available evidence to try to make educated guesses to improve patient outcomes. How could this be?" Hunter and Longo asked.

The answer, they said, comes from the need to reuse data from large studies like TAILORx, because such studies are too expensive to repeat every time there is a question—and the one asked in this new study will apply to many women. The commentators commend the TAILORx investigators for taking on the questions they have asked, and note, "Distinguishing between results that warrant a change in practice and those that do not will not lead to a 'precise' process." ◆

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CLINICAL FINDINGS

Maintenance Olaparib Aids PFS in *BRCA*-Mutated Metastatic Pancreatic Cancer, but Not OS

LANCASTER

PATIENTS WITH ADVANCED PANCREATIC cancer linked to germline genetic mutations did not see their disease worsen for an additional 3.6 months when treated with olaparib (Lynparza), but an early interim analysis did not show a statistically significant difference in overall survival (OS) either, according to recent study results.

The results of the subset of patients with germline mutations in the *BRCA1* and *BRCA2* genes were also published in the *New England Journal of Medicine*. Topline results were released in February.

Pancreatic cancer affects nearly 57,000 Americans annually; once it spreads, fewer than 10% of patients are alive 5 years after initial diagnosis. About 4% to 7% of patients with pancreatic cancer have a germline *BRCA* mutation.

The poly (ADP-ribose) polymerase (PARP) inhibitor olaparib is sold by Astra Zeneca and Merck. AstraZeneca and a grant from the National Institutes of Health funded the study.

The phase 3 study, called POLO (Pancreas Cancer Olaparib Ongoing), included 154 patients; 92 received olaparib at 300 mg twice a day and 62 received placebo. The 154 patients had confirmed *BRCA1/2* mutations via use of the BRACAnalysis CDx companion diagnostic from Myriad Genetics. It is currently the only FDA-approved test to find germline *BRCA1/2* mutations.

"The whole paradigm of precision medicine, is, indeed, to identify the 1 in 20 patients who carry a biomarker and offer them a drug."

—Johnathan M. Lancaster, MD, PhD

To be eligible for the randomized controlled trial, the patients had to have received at least 16 weeks of continuous first-line platinum-based chemotherapy, with no evidence of disease progression.

The primary end point of the study, median progression-free survival, was significantly longer in the olaparib group than in the placebo group (7.4 vs 3.8 months; hazard ratio [HR] for disease progression or death, 0.53; 95% CI, 0.35-0.82; $P = .004$).

At 24 months, 22% of the patients in the treatment group had not seen the disease progress compared with 9.6% of the placebo group.

Given the deadly nature of advanced pancreatic cancer, the fact that maintenance olaparib could stop progression for a few months for this group of patients "is really quite remarkable," said Johnathan M. Lancaster, MD, PhD, the chief medical officer for Myriad Genetics, in an interview with *The American Journal of Managed Care®*.

The interim analysis of OS, a secondary end point, showed no significant difference, with a median 18.9 months for the olaparib group and 18.1 months for the placebo group (HR for death 0.91; 95% CI, 0.56-1.46; $P = .68$). Patient-reported outcomes (health-related quality of life scores) were also not significantly different.

Lancaster said those results are not surprising given the crossover that can occur between different therapies; the study reported that 15% of the placebo group received a PARP inhibitor after disease progression.

"For the first time now, we have the opportunity to use precision medicine intervention to identify patients with pancreatic cancer [who] will likely benefit from PARP inhibition," he said.

There are a few reasons why the results are important, Lancaster said. POLO has clinical implications for a select group of patients who have few options, and it highlights not only the role of genetic testing for cancer in general but also for pancreatic cancer specifically, where *BRCA* is more well known for its role for breast and ovarian cancers for some populations. He also noted that the National Comprehensive Cancer Network updated its guidelines earlier this year to recommend universal germline *BRCA* testing for all patients with pancreatic cancer.

In addition, this study defines the potential and very nature of precision medicine, Lancaster said, despite the small numbers and percentages in the study.

"The whole paradigm of precision medicine, is, indeed, to identify the 1 in 20 patients who carry a biomarker and offer them a drug," as opposed to offering the drug to everyone, where, he said, "the effect is washed out."

Myriad announced earlier this year that it intends to seek FDA approval to use BRACAnalysis CDx as a companion diagnostic for olaparib in patients with pancreatic cancer; it is already used to identify patients with germline *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. It is also being studied in prostate cancer.

A first-in-class PARP inhibitor, olaparib is approved to treat multiple indications of advanced ovarian, fallopian, and metastatic breast cancer, including those with both inherited and acquired *BRCA* mutations. The *BRCA1* and *BRCA2* genes help cells repair DNA damage, and inherited mutations can make both women and men more likely to develop certain cancers. Olaparib works by blocking the DNA damage response in cells and tumors. ◆

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How Real-World Data Can Affect NSCLC Treatment

Samantha DiGrande

A NUMBER OF ABSTRACTS at the 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO) featured studies that focused on using real-world data to advance research and cancer care in non–small cell lung cancer (NSCLC).

"Now, what do we mean by real-world data? We mean data relating to patient health status or the delivery of healthcare routinely collected from a variety of sources including electronic health records, claims data, and more," explained Sumithra J. Mandrekar, PhD, of Mayo Clinic, during an oral presentation of the abstracts. "But that's different from real-world evidence, which is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from the analysis of real-world data."

The first presenter, R. Donald Harvey, PharmD, BCOP, FCCP, FHOPA, of the Winship Cancer Institute, discussed the results of a real-world study that surveyed the impact of broadening clinical trial criteria for patients with advanced NSCLC (aNSCLC).

He explained that the study utilized the guidelines put out by groups like the American Society of Clinical Oncology and Friends of Cancer Research for broadening eligibility criteria. The goal was to make the trial population more representative of what is seen in the real world and make the results more generalizable, as well as accelerate trial accrual.

The study found that using expanded criteria would enable nearly twice as many patients with aNSCLC to qualify and consider trial participation, and it would also likely result in trial participants who are more reflective of a broader patient population.

However, Mandrekar offered a note of hesitation when expanding trial criteria: "Sometimes expanding trial criteria actually leaves you with a lack of randomization. Randomization is critical for the success of a trial."

Interestingly, another study looked at a predictive model for determining 1-year survival in NSCLC based on electronic health records (EHRs) and tumor sequencing data available at the Department of Veterans Affairs (VA).

The cohort characteristics identified 365 patients who were older, predominantly male, and had a high rate of prior or current smokers. The study also found that a large number of patients in the cohort were classified as having stage IV NSCLC.

The genomic features of the predictive model defined binary features that reflected the presence or absence of variation in 96 genes that were included in both the EHR and tumor sequencing data, as well as the number of these genes that were present without variation.

"We were able to build an accurate predictive model of 1-year survival in patients with NSCLC at the VA, which integrates real-world clinical and genomic data," said Nathanael Fillmore, PhD, of the VA Boston Healthcare System. "This provides a good foundation to move forward in being able to offer support for clinical decision making for VA clinicians. However, the model does not yet include certain features, including weight loss and treatment details."

Another study was presented on utilizing big data to advance personalized therapies. Robert Doebele, MD, PhD, of the University of Colorado, began his presentation by first asking the question, "Is big data always best?" He offered an answer to his own question, explaining that sometimes using big data or big clinical trials can allow researchers to miss smaller, yet significant, findings.

He presented data from a study that enrolled 1692 patients and then broke that study out to just 9 patients with NSCLC. In a graph of all patients, all responses to the drug seemed to fall along the same curve. However, in the smaller cohort of patients, the data showed that this group actually had a "phenomenal response to the *EGFR* mutation," he said.

In keeping with the theme of ASCO's meeting this year, "Caring for every patient, learning from every patient," Doebele closed by saying that, "Models derived from large cohorts need robust data and, ultimately, need to be independently validated. Small data [have] ongoing merit and value for new discoveries, and with NSCLC especially, it can't be thought of as a single disease." ◆

#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 February 2018.
†Based on market share data from IMS from July 2014 to February 2018.

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 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% 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 24% of 1,011 patients exposed to IMBRUVICA® in clinical trials. 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 (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines.

Hypertension: Hypertension has occurred in 12% of 1,011 patients treated with IMBRUVICA® in clinical trials with a median time to onset of 5 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 (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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.

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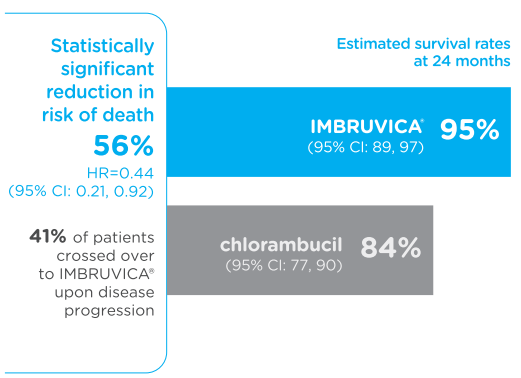
RESONATE™-2 FRONTLINE DATA

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

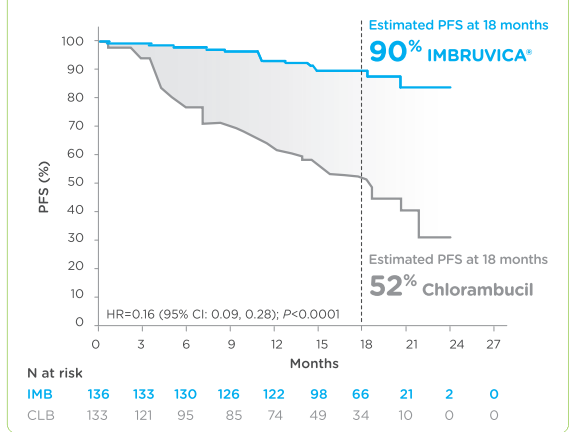


- Median follow-up was 28 months[2]
- Fewer deaths with IMBRUVICA® were observed; 11 (8.1%) in the IMBRUVICA® arm vs 21 (15.8%) in the chlorambucil arm[2]

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 estimable 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%)

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

ADVERSE REACTIONS

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, neutropenia (58%)*, diarrhea (42%), anemia (39%)*, rash (31%), musculoskeletal pain (31%), bruising (31%), nausea (28%), fatigue (27%), hemorrhage (23%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (36%)*, thrombocytopenia (15%)*, and pneumonia (10%).

Approximately 7% of patients discontinued IMBRUVICA® due to adverse reactions. Adverse reactions leading to discontinuation included hemorrhage (1.2%), atrial fibrillation (1.0%), pneumonia (1.0%), rash (0.7%), diarrhea (0.6%), neutropenia (0.6%), sepsis (0.5%), interstitial lung disease (0.3%), bruising (0.2%), non-melanoma skin cancer (0.2%), and thrombocytopenia (0.2%). Eight percent of patients had a dose reduction due to adverse reactions.

*Treatment-emergent decreases (all grades) were based on laboratory measurements and adverse reactions.

DRUG INTERACTIONS

CYP3A Inhibitors: Dose adjustments may be recommended.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe baseline hepatic impairment. In patients with mild or moderate 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 2018. **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)
560, 420, 280, 140 mg tablets | 140, 70 mg capsules

Brief Summary of Prescribing Information for IMBRUVICA® (ibrutinib)

IMBRUVICA® (ibrutinib) capsules, for oral use
IMBRUVICA® (ibrutinib) tablets, for oral use

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).

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.

Waldenström's Macroglobulinemia: IMBRUVICA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

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.

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 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to IMBRUVICA in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% 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 24% of 1,011 patients exposed to IMBRUVICA in clinical trials. *[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 (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to IMBRUVICA in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. See Additional Important Adverse Reactions.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias 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 has occurred in 12% of 1,011 patients treated with IMBRUVICA in clinical trials with a median time to onset of 5 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 (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with IMBRUVICA in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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 embryo-fetal 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]*
- Cardiac Arrhythmias *[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

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

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
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

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 (%)
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
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 three single-arm open-label clinical trials (Study 1118, Study 1121, and INNOVATE monotherapy arm) and one randomized controlled trial (INNOVATE) in patients with WM or MZL, including a total n=307 patients overall and n=232 patients exposed to IMBRUVICA. Study 1118 included 63 patients with previously treated WM who received single agent IMBRUVICA. Study 1121 included 63 patients with previously treated MZL who received single agent IMBRUVICA. INNOVATE included 150 patients with treatment naïve or previously treated WM who received IMBRUVICA or placebo in combination with rituximab. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received IMBRUVICA.

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

Seven percent of patients receiving IMBRUVICA across Studies 1118, 1121, and INNOVATE discontinued treatment due to adverse reactions. The most common adverse reactions leading to discontinuation were atrial fibrillation, interstitial lung disease, diarrhea and rash. Adverse reactions leading to dose reduction occurred in 13% of patients.

Study 1118 and INNOVATE Monotherapy Arm: 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 and 33 months in the INNOVATE Monotherapy Arm.

Table 9: Non-Hematologic Adverse Reactions in ≥ 10% in Patients with WM in Study 1118 and the INNOVATE Monotherapy Arm (N=94)

Body System	Adverse Reaction	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders	Diarrhea	38	2
	Nausea	21	0
	Stomatitis*	15	0
	Constipation	12	1
	Gastroesophageal reflux disease	12	0
Skin and subcutaneous tissue disorders	Bruising*	28	1
	Rash*	21	1
Vascular disorders	Hemorrhage*	28	0
	Hypertension*	14	4
General disorders and administrative site conditions	Fatigue	18	2
	Pyrexia	12	2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	21	0
	Muscle spasms	19	0
Infections and infestations	Upper respiratory tract infection	19	0
	Skin infection*	18	3
	Sinusitis*	16	0
	Pneumonia*	13	5
Nervous system disorders	Headache	14	0
	Dizziness	13	0
Respiratory, thoracic and mediastinal disorders	Cough	13	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 and the INNOVATE Monotherapy Arm (N=94)

	Percent of Patients (N=94)	
	All Grades (%)	Grade 3 or 4 (%)
Platelets Decreased	38	11
Neutrophils Decreased	43	16
Hemoglobin Decreased	21	6

INNOVATE: Adverse reactions described below in Table 11 reflect exposure to IMBRUVICA + R with a median duration of 25.8 months and exposure to placebo + R with a median duration of 15.5 months in patients with treatment naïve or previously treated WM in INNOVATE.

Table 11: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with WM in INNOVATE

Body System Adverse Reaction	IMBRUVICA + R (N=75)		Placebo + R (N=75)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Bruising*	37	1	5	0
Rash*	24	1	11	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	35	4	21	3
Arthralgia	24	3	11	1
Muscle spasms	17	0	12	1
Vascular disorders				
Hemorrhage*	32	3	17	3
Hypertension*	20	13	5	4
Gastrointestinal disorders				
Diarrhea	28	0	15	1
Nausea	21	0	12	0
Dyspepsia	16	0	1	0
Constipation	13	1	11	1
Infections and infestations				
Pneumonia*	19	13	5	3
Skin infection*	17	3	3	0
Urinary tract infection	13	0	0	0
Bronchitis	12	3	7	0
Influenza	12	0	7	1
Viral upper respiratory tract infection	11	0	7	0
General disorders and administration site conditions				
Peripheral edema	17	0	12	1
Respiratory, thoracic, and mediastinal disorders				
Cough	17	0	11	0
Blood and Lymphatic System Disorders				
Neutropenia*	16	12	11	4
Cardiac Disorders				
Atrial fibrillation	15	12	3	1
Nervous system disorders				
Dizziness	11	0	7	0
Psychiatric disorders				
Insomnia	11	0	4	0
Metabolism and nutrition disorders				
Hypokalemia	11	0	1	1

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

Grade 3 or 4 infusion related reactions were observed in 1% of patients treated with IMBRUVICA + R.

Study 1121: Adverse reactions and laboratory abnormalities described below in Tables 12 and 13 reflect exposure to IMBRUVICA with a median duration of 11.6 months in Study 1121.

Table 12: 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	43	5
	Nausea	25	0
	Dyspepsia	19	0
	Stomatitis*	17	2
	Abdominal pain	16	2
	Constipation	14	0
	Abdominal pain upper	13	0
	Vomiting	11	2
General disorders and administrative site conditions	Fatigue	44	6
	Peripheral edema	24	2
	Pyrexia	17	2
Skin and subcutaneous tissue disorders	Bruising*	41	0
	Rash*	29	5
	Pruritus	14	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	40	3
	Arthralgia	24	2
	Muscle spasms	19	3
Infections and infestations	Upper respiratory tract infection	21	0
	Sinusitis*	19	0
	Bronchitis	11	0
	Pneumonia*	11	10
Metabolism and nutrition disorders	Decreased appetite	16	2
	Hyperuricemia	16	0
	Hypoalbuminemia	14	0
	Hypokalemia	13	0
Vascular disorders	Hemorrhage*	30	0
	Hypertension*	14	5
Respiratory, thoracic and mediastinal disorders	Cough	22	2
	Dyspnea	21	2
Nervous system disorders	Dizziness	19	0
	Headache	13	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 13: 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 14 and 15 reflect exposure to IMBRUVICA with a median duration of 4.4 months in the cGVHD trial.

Table 14: 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	57	12
	Pyrexia	17	5
	Edema peripheral	12	0
Skin and subcutaneous tissue disorders	Bruising*	40	0
	Rash*	12	0
Gastrointestinal disorders	Diarrhea	36	10
	Stomatitis*	29	2
	Nausea	26	0
	Constipation	12	0
Musculoskeletal and connective tissue disorders	Muscle spasms	29	2
	Musculoskeletal pain*	14	5
Vascular disorders	Hemorrhage*	26	0
Infections and infestations	Pneumonia*	21	10
	Upper respiratory tract infection	19	0
	Sepsis*	10	10
Nervous system disorders	Headache	17	5
Injury, poisoning and procedural complications	Fall	17	0
Respiratory, thoracic and mediastinal disorders	Cough	14	0
	Dyspnea	12	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 15: 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: *Cardiac Arrhythmias:* In randomized controlled trials (n=1377; median treatment duration of 14.0 months for patients treated with IMBRUVICA and 7.5 months for patients in the control arm), the incidence of ventricular tachyarrhythmias (ventricular extrasystoles, ventricular arrhythmias, ventricular fibrillation, ventricular flutter, and ventricular tachycardia) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.2% versus 0% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of atrial fibrillation and atrial flutter of any grade was 8% versus 2% and for Grade 3 or greater was 4% versus 0.4% in patients treated with IMBRUVICA compared to patients in the control arm.

Diarrhea: Diarrhea of any grade occurred at a rate of 40% of patients treated with IMBRUVICA compared to 19% of patients in the control arm. Grade 3 diarrhea occurred in 3% versus 1% of IMBRUVICA-treated patients compared to the control arm, respectively. The median time to first onset was 21 days (range: 0 to 475) versus 47 days (range: 0 to 492) for any grade diarrhea and 77 days (range: 3 to 310) versus 194 days (range: 11 to 325) for Grade 3 diarrhea in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported diarrhea, 84% versus 88% had complete resolution, and 16% versus 12% had not reported resolution at time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution in IMBRUVICA-treated subjects was 6 days (range: 1 to 655) versus 5 days (range: 1 to 367) for any grade diarrhea and 6 days (range: 1 to 78) versus 19 days (range: 1 to 56) for Grade 3 diarrhea in IMBRUVICA-treated subjects compared to the control arm, respectively. Less than 1% of subjects discontinued IMBRUVICA due to diarrhea compared with 0% in the control arm.

Visual Disturbance: Blurred vision and decreased visual acuity of any grade occurred in 12% of patients treated with IMBRUVICA (10% Grade 1, 2% Grade 2, no Grade 3 or higher) compared to 6% in the control arm (5% Grade 1 and <1% Grade 2 and 3). The median time to first onset was 96 days (range, 0 to 617) versus 109 days (range, 2 to 477) in IMBRUVICA-treated patients compared to the control arm, respectively. Of the patients who reported visual disturbances, 61% versus 71% had complete resolution and 39% versus 29% had not reported resolution at the time of analysis in IMBRUVICA-treated patients compared to the control arm, respectively. The median time from onset to resolution was 31 days (range, 1 to 457) versus 29 days (range, 1 to 253) in IMBRUVICA-treated subjects compared to the control arm, respectively.

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 including acute and/or fatal events, hepatic cirrhosis
- 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, panniculitis
- 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.

Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term (such as anti-infectives for seven days or less) *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

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

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]*.

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 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.

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.

Data: 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. Pediatric studies have not been completed.

IMBRUVICA® (ibrutinib)

Geriatric Use: Of the 1011 patients in clinical studies of IMBRUVICA, 62% were ≥ 65 years of age, while 22% 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 severe hepatic impairment (Child-Pugh class C). The safety of IMBRUVICA has not been evaluated in patients with mild to severe hepatic impairment by Child-Pugh criteria.

Dose modifications of IMBRUVICA are recommended in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients for adverse reactions of IMBRUVICA closely *[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]*.
- *Cardiac Arrhythmias:* 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 oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day *[see Dosage and Administration]*.
- 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 doses to make up the missed dose *[see Dosage and Administration]*.
- 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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COST OF CARE

Outlining the Risks That Go Along With the Benefit of CAR T-Cell Therapy

Samantha DiGrande

ALTHOUGH CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy has been largely touted as one of the most important advances in cancer care in recent years, the therapy comes with the risk of severe toxicities as well as an increased financial burden due to the high cost of the drugs.

During the meeting, data were presented regarding "the other side of CAR T-cell therapy," namely, cytokine release syndrome (CRS), neurologic toxicity, and financial burden.

"[CAR T-cell therapy] is truly now the fourth arm of treatment for [patients with cancer] and has allowed our patients to get great therapeutic rewards," said Elizabeth Shpall, MD, of The University of Texas MD Anderson Cancer Center. "However, about half of the patients included in the study that was the basis of approval for Yescarta needed ICU [intensive care unit] management. In 3 of the published studies to date [for the therapies], almost all the patients developed some grade of cytokine release syndrome."

The authors of the study concluded that there are several factors that can predict the onset of CRS, such as a high marrow tumor burden, lymphodepletion using cyclophosphamide and fludarabine, and administering a higher CAR T-cell dose. Thrombocytopenia also seemed to be a predictor.

"So how can we ameliorate CRS? We need to focus on the identification of predictive biomarkers, prompt and correct use of anti-IL6 [interleukin-6] and steroid therapy, and educate our physicians extensively," Shpall said.

However, once a patient has hopefully overcome the week or so that CRS usually lasts, according to Shpall, the next challenge is to identify whether or not the patient has signs of neurotoxicity, which can often occur after CRS resolves.

"The immediate first fever happens early. That's usually the first sign, if a patient develops a fever early on. Overwhelmingly, though, neurotoxicity is reversible and usually subsides within 7 days," said Bianca Santomasso, PhD, MD, of Memorial Sloan Kettering Cancer Center.

Historically, Santomasso explained, neurotoxicity used to be included in CRS. But when studying the toxicity, it began to be identified by different characteristics, such as global encephalopathy and aphasia, among others.

"We've definitely learned some lessons and figured out what to look for when it comes to neurotoxicity. We know that we need to do a baseline MRI [magnetic resonance imaging], watch a patient's vitals and electrolytes, and definitely a declining level of consciousness without another cause is concerning," said Santomasso.

Putting aside the physical cost of the therapies, the actual price of the therapies can be cause for patient concern as well, considering the price of the 2 FDA-approved therapies currently on the market are $495,000 and $373,000.

"Currently, there are 475 cell and gene therapy companies in North America. In 2018, there were about $20 billion worth of cell therapy deals, IPOs [initial public offerings] of nearly $1 billion, and $750 million in company series funding," said Carlos Bachier, MD, of the Sarah Canon Center for Blood Cancer. "And yet, if you take out the university programs and big cancer centers, there are only 17 community institutions left that administer CAR T-cell therapy."

It is important to note that while the cost to the patient is significant, the cost to the institution is also substantial. In order to be able to administer the therapy, the institution must have a triage CAR T nurse or coordinator, train its medical staff on CAR Ts, have the proper collection/shipping/storage containers for the product, and ensure proper reporting to the FDA in order to allow for proper regulation.

"Best practices of experienced centers include building a multidisciplinary team that not all institutions are prepared or capable of implementing…[and] financial barriers for both the patient and the institution providing the therapies can prevent wide use of the treatments," said Bachier.

To date, reimbursement has not been finalized for these products, and is currently being discussed by CMS. ◆

Oncology Reimbursement Reform Leaves Stakeholders With More Questions Than Answers

ONCOLOGISTS AND REPRESENTATIVES from UnitedHealthcare and the Center for Medicare and Medicaid Innovation (CMMI) took the stage at the 2019 Annual Meeting of the American Society of Clinical Oncology to discuss oncology reimbursement reform and possible changes on the horizon for the promotion of higher-value care.

Jennifer Malin, MD, PhD, FASCO, senior medical director of oncology and genetics at UnitedHealthcare, started off the session by explaining what oncologists and patients already know: Healthcare costs are unsustainable.

"When we talk about the cost in healthcare, oftentimes we focus on just the pricing of the drugs and what individual out-of-pocket costs are. But the overall impact on the total cost of care is what impacts people's premiums and what the federal or state government has to pay for Medicaid. That impacts the overall affordability for people to buy insurance in the first place," said Malin.

She then reviewed some strategies oncologists are all too familiar with that payers use to improve the value of cancer therapy, such as clinical pathways, episode-payment shared savings, bundled payments, and shared-risk capitation.

UnitedHealthcare utilized each of these strategies in creating their own cancer episode program. The program, first implemented by Malin's predecessor Lee Newcomer, underwent a proof-of-concept pilot study from 2009 to 2012. Afterward, results showed that the program had a 34% reduction in costs for the 5 practices that were enrolled.

"Our cancer episode program is a new payment model based on the treatment of cancer episodes instead of drug margins. The program removes an oncology practice's dependency on drug margins and rewards physicians for improved quality and reduction in the total cost of cancer treatment. It also builds a learning system to identify best practices for improved quality and value," she said.

After the results of the initial pilot, UnitedHealthcare rolled the program out to 250 practice sites. Due to the larger number of practices enrolled, collaboration between UnitedHealthcare and the practices went from monthly interactions in the pilot to less often. This, in part, contributed to the lower amount of savings—13%—seen once the program expanded.

In talking about the revolution toward value-based care, the faults with traditional fee-for-service (FFS) programs are often discussed. Karen Hoffman, MD, MPH, of The University of Texas MD Anderson Cancer Center, presented provocative data regarding practices that use FFS costing more money and more often referring their patients for more expensive treatments.

"In a model where physicians and healthcare providers are reimbursed for each service rendered, it may provide financial incentives to increase utilization of services or recommend services that are more expensive," said Hoffman.

She explained that while physicians are prohibited by national statute from referring Medicare patients for designated health services at entities with which they have a financial relationship, study results show more services are used by physician "owners" versus nonowners.

"Specifically, the data show that there is an increase in anatomic pathology services by self-referring providers. In 2010, it was estimated that self-referring providers made 918,000 more referrals for pathology, which ended up costing Medicare $69 million," she said.

Finally, Lara Strawbridge, MPH, of CMMI, presented about an effort to address costs that oncologists are quite familiar with: the Oncology Care Model (OCM).

The OCM, which was implemented in 2016 as a 5-year model, is an episode-based payment model that targets chemotherapy and related care during a 6-month period that begins with a patient's receipt of chemotherapy.

"The OCM has 176 practices, about 7000 practitioners, and sees 200,000 unique beneficiaries per year, with 260,000 episodes of care per year," said Strawbridge.

She provided an overview of some of the positive outcomes of the program, including an anecdotal story from a provider saying that "[the OCM] enables us to provide the care we've always wanted to do." However, as the program nears the end of its 5-year pilot phase and CMMI looks to implement changes for the next version of the program, what spoke louder in Strawbridge's presentation were the unanswered questions.

The OCM has generated a lot of actionable, valuable data for practices, although this has come at a cost of a high administrative reporting burden. Strawbridge didn't mention those reporting burdens when discussing the challenges the OCM has seen over the past few years. What was mentioned, such as the limitations of the Medicare claims system and the complexity of practice business and coding models, are multifaceted issues that may not be addressed by the next rendition of the program.

For example, in a recent meeting of the Institute for Value-Based Medicine®, Jessica Walradt, manager of Managed Mare of Government Programs, Value-Based Care at Northwestern Memorial Healthcare, explained there's a lot of confusion around how episodes are triggered with the OCM due to an episode starting at the receipt of chemotherapy. This is because patients could be administered chemotherapy as maintenance therapy as well as an active treatment. Due to this, Waldradt said her institution is sometimes unsure which patients are even meant to be included in the OCM.

This too, was not mentioned by Strawbridge.

In terms of the future of the OCM, much remains unclear.

Strawbridge said, "We're working on the next version of the model to include further improvement in quality of care and health outcomes, moving farther away from fee-for-service infrastructure for payments, considering chemotherapy and supportive care, and looking into the adoption of 2-sided risk." ◆

MALIN

STAWBRIDGE

NEWCOMER

Articles by Samantha DiGrande

ASCO Town Hall Brings Tense Conversation on Drug Pricing

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) held a town hall meeting to discuss drug pricing at its 2019 meeting, with moderator Jeffrey Ward, MD, FASCO, hematologist at the Swedish Cancer Institute, joining Rodney Whitlock, PhD, of McDermott+Consulting.

Drug pricing seemed like an appropriate topic for ASCO's town hall as the Trump administration has made lowering the cost of medications a major objective. The administration has put out a series of proposals looking to address the cost of drugs, such as the International Pricing Index (IPI) and the recently finalized rule around direct-to-consumer advertising for pharmaceutical companies.

"What we have is 3 types of issues out there that you see policymakers discussing," Whitlock said. "There are blockbuster drugs coming out with significant price tags attached, speculation issues around astronomical drug price increases given the 'villian' made-for-our-time Martin Shkreli, and finally, there're regular drug price increases where drug companies raise their prices in January. Why? Because it's January. And then again in June. Why? Well, because it's June."

However, the issue of drug pricing has not yet been linked to a single direct, surefire cause. It's no secret that patients are feeling the effects of out-of-pocket costs of drugs, whether it's in co-pays or co-insurance costs, but who is to blame? "There's a tremendous amount of 'not it' and finger pointing going on. Drug makers want you to believe that the issues are the $700 aspirins at the hospital—that it's everyone but them. But on the other side, you see other stakeholders who set the prices and they're also saying it's not them, but we don't know because it's not a transparent system," he said.

When asked if he believes the politics will change around whether the government should have a place in instituting drug prices, Whitlock said there's definitely renewed interest in and openness now to say that if the marketplace isn't working for consumers under the current system, then the government will come in and set pricing.

"An example would be, look what's happening with surprise billing. Congress has given that great interest, and once they heard about it, they took it on and basically said, 'Well then, let's just stop this right now,'" said Whitlock. "It's a gateway drug to larger price controls. Once you do it there, can't you go other places to set price controls? I mean, the government has been doing that in the Medicare space for quite some time now."

Regarding the IPI model, Whitlock offered a word of caution for what the drug companies' response to such a model would be. He hypothesized whether the companies would try to get underneath the IPI and raise costs in other countries, so as to not lose money in the United States, or would they simply accept the lower payments?

"[This is something] that hasn't been discussed with this issue. It's the point that there is clearly a trade issue at hand here. Other countries are able to tell drug companies, 'You have to sell at this price to sell in our countries.' Now, yes, drug companies could get out of [the problem the IPI poses] by raising the prices in other countries. But what isn't being addressed—and this is truly a trade issue—is the inability of drug companies to raise prices in other countries even a nickel," said Whitlock.

The question remains, "What will the administration do regarding the IPI? Although there was a final rule put out, it has yet to take an effect. Whitlock floated the notion that the administration is using this proposal, and others, as a bargaining chip for what may come together in the fall as a larger deal with Congress. Perhaps not. Either way, Whitlock stressed that healthcare stakeholders need to pay attention to what's happening in Washington, DC, and stay clued in as to what's to come. "As they say, if you're not at the table, you're on the table."

A town hall convened at the annual meeting of the American Society of Clinical Oncology to discuss drug pricing drew intense interest.

In an attempt to bring the conversation back to the oncology stakeholders in the room, Michael Kolodziej, MD, vice president and chief innovation officer at ADVI Health, Inc, poised his question in earnest: "We, as oncologists, are floating on the Titanic, and we're worried about what next song the orchestra will play because all of the stuff we've been doing forever is going to become incredibly irrelevant as we move into combination I-O [immuno-oncology] therapy, CRISPR [Clustered Regularly Interspaced Short Palindromic Repeats], and CAR T [chimeric antigen receptor T-cell therapy]. These are therapies that will cost, per patient, $500,000 to $1 million…. Help me understand why we're not interested in pursuing outcomes-based contracting—through a model, through legislation, anything—because as we move technology forward, and the prices will go up with that advance, we need to find a way to pay for it."

Whitlock's response largely explained what healthcare stakeholders already know: Policymakers really don't understand how this world works. "The core mission of the FDA in approving a drug is safety and efficacy. That's it. The FDA is not in any way tasked to determine whether or not drugs have comparative value or that they meet a certain outcome-based type metric. CMS, their core task is to pay the freaking bills," he said. "So, when you talk about the 2 federal agencies most capable of engaging the conversation you just raised—which is critically important—you first need to grasp how utterly [incapable] they are at raising the conversation, because they don't have the skill set to do it."

Rather than taking on the challenge and bringing the suggestion back to Washington, DC, Whitlock called on the stakeholders in the room and ASCO members to push the conversation forward. "Moving in the direction of value, we are so far removed from that. Don't wait on the federal government. If you, as an organization, want to drive that conversation, you're better equipped than waiting for someone else at the 'mothership' in Baltimore where CMS is located, to come up with the idea," Whitlock said. ◆

The Importance of Including Primary Care Physicians in a Patient's Cancer Journey

"HOW DO YOU CURRENTLY collaborate with your primary care colleagues in caring for patients with cancer?" This was how Larissa Nekhlyudov, MD, MPH, opened the session, "Bringing the Primary Care Physician Back Into Cancer Care."

Answers to Nekhlyudov's question ranged from communication through electronic health record (EHR) systems to picking up the phone and calling the primary care physician (PCP). One thing remained consistent throughout every answer: We need to be doing better.

Nekhlyudov was joined by panelists Piyush Srivastava, MD, gastrointestinal medical oncologist at Kaiser Permanente; Trevor Jolly, MBBS, medical oncologist at UNC Health Care; and Elizabeth Schiff, a patient advocate and 2-time cancer survivor, to discuss and present interactive case studies in which PCPs should be a part of the conversation.

The first case involved a 75-year-old post-menopausal female with newly diagnosed, screen-detected, left-sided invasive breast cancer; her medical history included a body mass index of 31.4 and several years of hypertension. The audience and panelists were asked which medical condition was most likely to cause the patient's death in the next 10 years. Most answered cardiovascular disease, as one of the highest risk factors for cardiovascular disease is hypertension. When the audience was asked who they would prefer to manage the patient's blood pressure and other cardiovascular disease risk factors, a cardiologist or a PCP, most preferred a PCP.

This surprised Nekhlyudov, who expected most audience members to recommend a cardiologist. She presented data from a study published in *JAMA* in February 2019, which showed that PCPs "have a huge effect on mortality for [patients with cancer]. Every 10 additional PCPs per 100,000 population is associated with 51.5 extra days of life expectancy versus 19.2 days for additional specialists. Also, every 10 additional PCPs per 100,000 population was associated with reduced cardiovascular, cancer, and respiratory mortality by 0.9% to 1.4%," said Nekhlyudov.

Jolly couldn't agree more regarding the importance of a PCP in the journey of a patient with cancer. He explained that what he often sees in practices is that the oncologist will let the PCP deal with the hypertension and the oncologist will deal with the cancer, as with the case study. "But we need to collaborate more. If you see that your patient has hypertension, call her physician. Bring it to their attention. Ask them to follow up, if you started her on a hypertension medication. That communication is key."

Although the panelists and the audience seemed to agree on this matter, 1 audience member brought up a point that had not yet been mentioned: "You haven't addressed the medical economics of these visits. Some patients have a co-pay, and they can't afford to see their primary care physician as often as they see their oncologist during active treatment."

Schiff agreed. Having been through her own cancer journey, she explained that she knew the care coordination could get complicated. "If you need to choose between seeing your oncologist and seeing your PCP, well, that would be hard. If you're in active treatment, I would imagine you'd see your oncologist. But this is where the communication between the oncologist and the PCP is essential. If the patient can only economically see the oncologist on a regular basis, that oncologist needs to communicate with the PCP to make sure they're kept up-to-date on the patient's treatment journey and condition."

When asked to describe ways to improve communication between PCPs and oncologists, the overarching responses included creating an integrated EHR system across the providers and needing more time to meet with each patient. ◆

Cannabis Risks and Benefits in Cancer Symptom Management: Much Remains Unknown

DAVIS

CYR

WORSTER

BRAUN

OPEN CHAIRS WERE SCARCE as a session titled "Is There a Role for Cannabis in Cancer Symptom Management?" was set to begin. The session featured knowledgeable oncologists Mellar Davis, MD, of Geisinger Health System; Claude Cyr, MD, of McGill University; Brooke Worster, MD, of Thomas Jefferson University; and Ilana Braun, MD, of Dana-Farber Cancer Institute.

Oncologists, patient advocates, patients, and other stakeholders from around the world gathered to hear different perspectives regarding the use of cannabis in symptom management for patients with cancer. Panelist after panelist went up to present available data, and each reiterated the same point: We need more research.

As it stands right now, the legal landscape of cannabis use, particularly in the United States, is puzzling, to say the least. At the time of the presentation, 33 states have some form of legal marijuana. Of these, 10 offer a parallel recreational law, 14 have approved only limited medical use, and only 3 fully prohibit it. Federally, however, marijuana remains a Schedule 1 drug, which deems that it offers "no acceptable medical use, lacking [a] safety profile acceptable for use under medical supervision, and a high abuse potential," according to Braun.

"Cannabis is commonly used by patients during cancer therapy, frequently without the oncologist's knowledge. How cannabis influences cancer therapy and cancer course is completely unknown."

—Mellar Davis, MD

This creates problems in terms of prescribing, administering, and even researching the drug. Additionally, it presents a problem for patients with cancer who do want to access it—sometimes with the permission or urging of their healthcare provider. These same patients might walk into a dispensary and be offered products that have not gone under FDA review for safety, efficacy, or potency.

"Cannabis is commonly used by patients during cancer therapy, frequently without the oncologist's knowledge," said Davis. This presents a problem because, as each panelist pointed out, "how cannabis influences cancer therapy and cancer course is completely unknown."

Cyr began his presentation by taking a poll of the audience. He asked, "How many people feel uncomfortable offering cannabis to patients?" Although a decent number of oncologists raised their hands, it was noted that there were significantly fewer than in recent years. He then asked the audience why they were uncomfortable, and the response was largely that they were waiting for more evidence.

The legal landscape of medical cannabis is puzzling, as laws in most states differ from federal policy.

Cyr's presentation was somewhat unconventional by usual standards of cannabis use in patients with cancer. He explained that many of the most common adverse events (euphoria, aversive memory extinction, slowed down sense of time, and relaxation, among others) could actually be positive for patients with cancer.

"If you have a patient who is nearing end of life, who is feeling extremely depressed, well cannabis may be the safest drug to prescribe that elicits euphoria," he said. "Though aversive memory extinction may seem like a bad thing for other patients, I would offer that cancer patients may not want to remember every minute of sitting through chemotherapy. And for patients who consistently report feeling like their lives are slipping away from them and that they don't have much time left, a slowed down sense of time could be a great thing."

Although the available research is mixed regarding the risks and benefits of cannabis use in patients with cancer, Worster works with the geriatric population and stressed that she has some different concerns than her colleagues working with younger patients with cancer.

"Age is just a number. There are large differences in the rate of aging, and different organ systems age at different rates. An individual's age, per se, is not the problem; however, it does raise the statistical likelihood of certain events—such as falls—if patients are initiating cannabis use," she said.

In this population, she explained, adverse events of cannabis use, such as dizziness, could have life-threatening consequences.

When moving forward in this space, although the law conflicts across states, as well as federally, Braun offered a few closing thoughts: "Healthcare providers should become versed in the endocannabinoid system the same way we're versed in other systems. Cannabis' benefits and risk should be included in medical education and CME [continuing medical education] curricula. Medical infrastructure should take medical marijuana into account. Everyone should advocate for loosening of restrictions on medical marijuana clinical trials, and professional societies, such as the American Society of Clinical Oncology, should develop consensus guidelines either for or against the prescribing of these products." ◆

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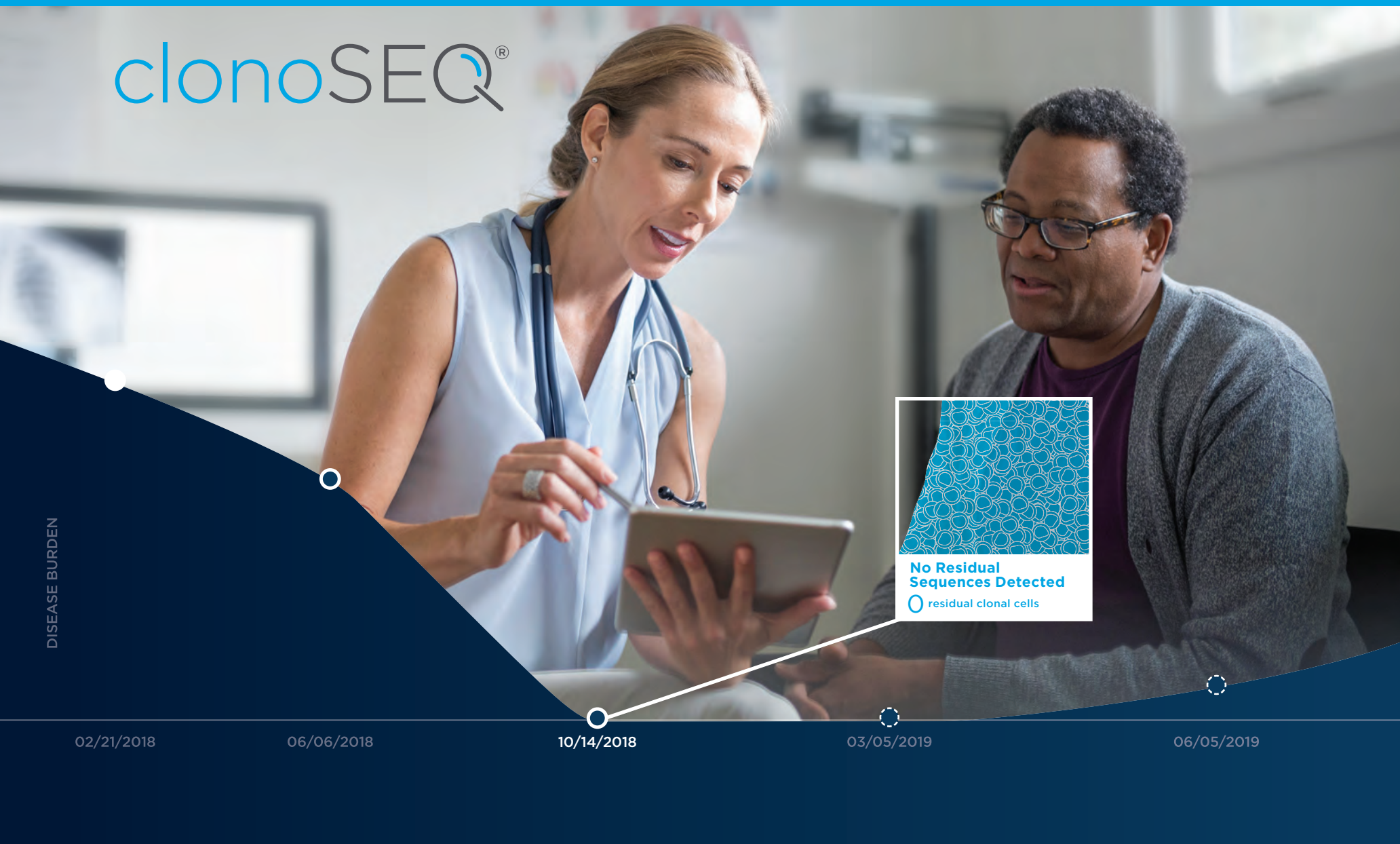

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Articles by Kelly Davio

Researchers Report on 3 Bevacizumab Biosimilar Development Programs

THE ANTI–VASCULAR ENDOTHELIAL growth factor (anti-VEGF) agent bevacizumab (Avastin) carries indications for lung cancer, colorectal cancer, breast cancer (in Europe), and glioblastoma, and has been the target of multiple hopeful biosimilar challengers, 2 of which are approved. Three developers reported on their progress with developing biosimilars of this anticancer agent.

ABP 215 (MVASI)

The first bevacizumab biosimilar to be approved by the FDA and authorized by the European Commission, ABP 215 (Amgen's MVASI), earned the FDA's clearance on the basis of data that included findings from the phase 3 MAPLE study, which compared the biosimilar to the reference in patients with advanced nonsquamous non–small cell lung cancer (NSCLC).

During the meeting, researchers reported on the totality of the evidence on ABP 215 that led to approval.[1]

The researchers compared VEGF-A kinetic parameters for common isoforms: 121, 165, and 189. They determined that binding to all 3 isoforms was similar for the biosimilar and the reference product.

Patients were randomized to receive the biosimilar (n = 328) or the reference (n = 314) with carboplatin and paclitaxel for up to 6 cycles, and efficacy was based on objective tumor assessments. The primary efficacy end point was the risk ratio of objective response rate (ORR), and clinical equivalence was confirmed if the 2-sided 90% CI of the risk ratio (RR) was within the prespecified margin of 0.67 to 1.5.

Based on a central analysis, ORR was achieved in 39.0% of patients in the biosimilar arm and in 41.7% of patients in the reference arm (ORR risk ratio, 0.93; 90% CI, 0.80-1.09). Based on an investigator analysis, ORR was achieved in 47.9% of patients in the biosimilar arm and in 48.1% of patients in the reference arm (ORR risk ratio, 1.01; 90% CI, 0.88-1.16).

These results, wrote the authors, further confirm the similarity of ABP 215 to its reference, and support the extrapolation to all available indications for bevacizumab.

IBI305

Innovent provided greater detail on its phase 3 comparative study in patients with NSCLC after having announced positive topline results of the study in December 2018.

In the newly reported data, Innovent said that 450 patients with NSCLC who were receiving first-line treatment with carboplatin and paclitaxel were randomized to receive either the proposed biosimilar (n = 224) or the reference bevacizumab (n = 226) until progression.[2]

The primary end point was ORR, evaluated by comparing the 2-sided 90% CI of the risk ratio between the study arms. The prespecified equivalence margin was 0.75 to 1.33.

ORR in the full analysis set was 44.3% in the biosimilar arm and 46.4% in the reference arm; the RR for ORR was 0.95 (90% CI, 0.803-1.135), which fell within the prespecified margin.

Medium progression-free survival was 8.4 months in the biosimilar arm and 8.3 months in the reference arm. Treatment-emergent adverse events were balanced between arms and consistent with the known profile of bevacizumab.

The incidence of antidrug antibodies (ADAs) was 0.5% in the biosimilar arm and 0% in the reference arm, and no patients developed neutralizing antibodies.

MB02

Finally, researchers reported that the STELLA trial of MB02—a proposed bevacizumab biosimilar being developed by mAbxience—is underway.[3]

Three biosimilar programs for the anti-VEGF agent bevacizumab reported on their progress at ASCO.

The study is a multinational, double-blind, randomized, parallel-group, equivalence study to compare the efficacy and safety of the biosimilar versus its reference, both in combination with plus chemotherapy in patients with stage IIIB to IV NSCLC

Patients will be randomized to the biosimilar or the reference along with chemotherapy, and after 6 cycles, they will receive bevacizumab monotherapy every 3 weeks until progression, intolerance, death, withdrawal, or the end of the study. The primary objective is to compare the ORR between arms at week 18. Progression-free survival and overall survival at weeks 18 and 52, safety, and immunogenicity will also be assessed.

A sample size of 600 was calculated to provide 89% power to show equivalence on a primary end point of RR based on ORR, and 596 individuals have been recruited, say the investigators. ◆

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No Significant Difference in EFS, OS Between Herceptin and Biosimilar, Ontruzant, at 3 Years

SAMSUNG BIOEPIS' SB3 (ONTRUZANT) has been approved in the United States and European Union as a biosimilar of the brand name trastuzumab, Herceptin. Approval relied in part on a phase 3 study comparing the biosimilar with the reference in women with *HER2*-positive early or locally advanced breast cancer in the neoadjuvant setting. [1]

Notably, some of the lots of the reference trastuzumab that were used in the study—with expiry dates from August 2018 to December 2019—had been impacted by a product shift that resulted in downward changes to antibody-dependent cell-mediated cytotoxicity (ADCC).

At the time, ADCC was not fully understood to be key to the efficacy of trastuzumab. However, in results that were presented in late 2018 at the San Antonio Breast Cancer Symposium, the importance of this quality attribute and its impact on event-free survival (EFS) came into clearer focus.

According the 2018 study data, 126 patients had been exposed to at least 1 lot of reference trastuzumab that had lower ADCC activity.[2] Another 55 patients given the reference therapy were not exposed to these lots. After a median of 30.1 months of treatment with the biosimilar—which was given to 186 patients—and 30.2 months of treatment with the reference which was administered to 181 patients, there was no statistically significant difference in EFS between the biosimilar arm (96.7%) and the patients who were not exposed to the lower-ADCC activity lots of the reference (98.2%). However, in the patients exposed to the lower-ADCC activity reference, 2-year EFS was lower (92.5%).

Researchers presented the 3-year results of an evaluation of survival by ADCC status.[2]

At a median follow-up of 40.8 months in the biosimilar arm and 40.5 months in the reference arm, EFS rates were 92.5% in the biosimilar arm, 94.5% among patients treated with the reference who were not exposed to the lower-ADCC activity lots, and 82.5% among patients who were exposed. Overall survival (OS) rates were 97.0%, 100%, and 90.6% in the 3 groups, respectively.

Among those treated with the reference, exposure was associated with decreased EFS compared with no exposure (hazard ratio [HR], 0.14; 95% CI, 0.04-0.51; $P = .003$). Decreased OS was noticed as a trend in the exposed group compared with the unexposed group, but no significant difference emerged (HR, 0.14; 95% CI, 0.02-1.15; $P = .068$).

Between patients treated with the biosimilar and those treated with the reference product who were not exposed to the lower-ADCC lots, no difference was observed in EFS (HR, 1.06; 95% CI, 0.33-3.44; $P = .923$) or OS (HR, 0.54; 95% CI, 0.05-5.44; $P = .600$).

The investigators concluded that patients exposed to the lower-ADCC lots of the reference had significantly lower EFS than those who were not exposed, whereas the biosimilar-treated patients and those unexposed to the affected lots had no significant differences in EFS or OS. ◆

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Biosimilar Pegfilgrastim Can Increase Access, but Patient Perception Remains a Barrier

BIOSIMILAR PEGFILGRASTIM, of which 2 brands (Mylan's Fulphila and Coherus BioScience's Udencya) have become available in the United States recently, is listed at a discount of 33% to the reference product, Amgen's Neulasta.

Researchers said that, for payers with large populations, the discounted biosimilar pegfilgrastim can produce substantial cost savings that "can be applied to offer increased access to supportive care."

The research team, from biosimilar developer Sandoz, which is developing its own biosimilar pegfilgrastim, used a cost minimization model based on a hypothetical group of 20,000 patients.[1] They used the average selling price, obtained from payment allowance limits in the first quarter of 2019, for prophylaxis of febrile neutropenia for 1 chemotherapy cycle.

The simulation included a calculation of cost minimization per cycle when patients were converted from the reference pegfilgrastim to a biosimilar on a ratio of 10% to 100% and at a discount of 15% to 35%. Expanded access to biosimilar pegfilgrastim was calculated based on budget neutrality.

Per-cycle per-patient cost minimization of converting from reference pegfilgrastim to the biosimilar ranged from $702.27, representing a 15% discount, to $1638.63, representing a 35% discount. For the total 20,000 patients, these savings totaled more than $14 million at a 15% discount to $32 million at a 35% discount for a 100% conversion rate. If half of patients were prescribed the biosimilar, it was estimated that savings could range from more than $7 million at the 15% discount to more than 16 million at the 35% discount.

If 100% of patients were prescribed the biosimilar at the 15% discount, an additional 3529 patients could be treated with the savings generated. If half of the patients were prescribed the biosimilar, the savings could be applied to treat 1765 patients at the same discount. Assuming a 35% discount, 50% biosimilar use would produce savings that could allow 5385 patients to be treated.

For payers with sizable populations, biosimilar pegfilgrastim offers an opportunity to provide increased access on a budget-neutral basis, according to the researchers.

Despite the budgetary benefits of biosimilar pegfilgrastim being clear from the payer perspective, patients may continue to have concerns about receiving a biosimilar rather than its reference. Also during the meeting, another research team published findings that, although a majority of patients with cancer do not believe that more costly drugs work better than cheaper alternatives, they may have residual concerns about cost-saving drugs when used in cancer care.[2]

The researchers surveyed a sample of 75 patients with cancer in clinics and an infusion center, asking questions about cost and patient participation in

continued ▸

decision making about treatment options. In total, 66% of respondents said they did not believe that more costly medicines were more effective than less costly ones for the same disease. However, just 60% of that group, and 44% of the overall group, said they preferred that their doctor prescribe a cheaper drug for them.

Among respondents who expressed a belief that more expensive drugs are not more effective but wanted to receive a more expensive drug anyway, 8 respondents indicated that they believed cancer to be too serious to take chances, 5 wanted the most expensive drug covered by insurance, and 2 said they wanted the best possible medication available.

Additionally, 90.67% said they wanted to be informed if their physician was prescribing a less expensive version of their therapy.

According to the authors, patients have lingering concerns that cost savings may be a proxy for quality, particularly in cancer indications. Overcoming these perceptions will be crucial, they indicate, if cost savings are to be possible. ◆

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Phase 3 and Postmarketing Data Support the Efficacy and Safety of Biosimilar Trastuzumab, Ogivri

MYLAN AND BIOCON'S TRASTUZUMAB biosimilar, Ogivri, was the first biosimilar referencing Herceptin to be approved by the FDA. Approval of Ogivri was based in part on data from the phase 3 HERITAGE trial, a double-blind, randomized clinical trial that evaluated the biosimilar in patients with *HER2*-positive metastatic breast cancer without prior chemotherapy or trastuzumab for metastatic disease.

Data from the HERITAGE study, reported elsewhere, show that the biosimilar was equivalent to the reference trastuzumab when given in combination with a taxane as first-line therapy, as measured by 24-week overall response.[The safety profile of the biosimilar was also comparable to that of the reference Herceptin.[1]

Researchers presented the final overall survival (OS) results from HERITAGE.[2]

> **"The safety data are consistent with the profile of the reference trastuzumab, and no new safety signals were detected."**
>
> —study authors

After 24 weeks, the 343 patients who had responding or stable disease continued to receive trastuzumab as monotherapy according to their initial randomization to either the biosimilar (n = 179) or the reference (n = 164). Also included in the results were safety and OS during maintenance, through 36 months of follow-up from the last patient on the study.

The mean time to discontinuation was 19 months in both the biosimilar arm and the reference arm. Treatment-emergent adverse events (AEs) during monotherapy were similar in the biosimilar arm (69%) and the reference arm (73%). Serious AEs occurred in 6% of patients in both groups.

At 36 months, 169 patients had received additional lines of therapy, with a similar distribution of *HER2* treatments, endocrine therapies, and chemotherapies.

Final median progression-free survival was 11.1 months in both of the arms. The median duration of response was 9.9 months in the biosimilar arm and 9.8 months in the reference arm. OS was 35.0 months and 30.2 months in the 2 arms, respectively.

In addition to these data from HERITAGE, separately, another research group shared its research on postmarketing surveillance of Ogivri: their results show that the safety of the biosimilar is consistent with that of the reference.[3]

The biosimilar, although not yet launched in the United States, is available in other markets, including Brazil, where it is subject to inclusion in the manufacturer's patient support program to monitor AEs. The authors of a prospective observational study used data from the program, which covered 21 patients with *HER2*-positive breast cancer who enrolled in the program between May 2018 and January 2019.

In total, 16 patients reported 101 AEs, 7 of which were serious. The most frequently reported AEs were general disorders and administration-site conditions, followed by nervous system disorders and gastrointestinal disorders. The most-reported symptoms were nausea, asthenia, infusion-site reactions, paresthesia, and pain.

According to the investigators, these safety data are consistent with the profile of the reference trastuzumab, and no new safety signals were detected. ◆

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Fulphila®
(pegfilgrastim-jmdb) injection

The First FDA-approved Biosimilar for Neulasta® (pegfilgrastim)

INDICATION

Fulphila® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Fulphila® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

IMPORTANT SAFETY INFORMATION

Do not administer Fulphila® to patients with a history of serious allergic reactions, including anaphylaxis, to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila®.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila® for ARDS. Discontinue Fulphila® in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure and can recur within days after discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila® in patients with serious allergic reactions to any pegfilgrastim or filgrastim products.

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue if sickle cell crisis occurs.

Glomerulonephritis has been reported in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Fulphila®.

White blood cell counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of CBCs during therapy with Fulphila® is recommended.

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor (G-CSF) administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

The G-CSF receptor, through which pegfilgrastim and filgrastim products act, has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology and discontinue Fulphila® if aortitis is suspected.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

Mylan®

FULPHILA® (pegfilgrastim-jmdb) injection, for subcutaneous use

Initial U.S. Approval: 2018

Brief summary. See package insert or full prescribing information.

INDICATIONS AND USAGE

Patients with Cancer Receiving Myelosuppressive Chemotherapy

Fulphila is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies]*.

Limitations of Use

Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

CONTRAINDICATIONS

Fulphila is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products *[see Warnings and Precautions]*. Reactions have included anaphylaxis *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila, for ARDS. Discontinue Fulphila in patients with ARDS.

Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila in patients with serious allergic reactions. Do not administer Fulphila to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

Use in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Fulphila if sickle cell crisis occurs.

Glomerulonephritis

Glomerulonephritis has occurred in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dosereduction or interruption of Fulphila.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue Fulphila if aortitis is suspected.

Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

ADVERSE REACTIONS

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

- Splenic Rupture *[See Warnings and Precautions]*
- Acute Respiratory Distress Syndrome *[See Warnings and Precautions]*
- Serious Allergic Reactions *[See Warnings and Precautions]*
- Use in Patients with Sickle Cell Disorders *[See Warnings and Precautions]*
- Glomerulonephritis *[See Warnings and Precautions]*
- Leukocytosis *[See Warnings and Precautions]*
- Capillary Leak Syndrome *[See Warnings and Precautions]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells *[See Warnings and Precautions]*
- Aortitis *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n =56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, place-bo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m^2 every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3

Body System Adverse Reaction	Placebo (N = 461)	Pegfilgrastim 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100 x 10^9/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to pegfilgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL. Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of pegfilgrastim products. 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.

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing *[see Warnings and Precautions]*
- Sickle cell crisis *[see Warnings and Precautions]*
- Glomerulonephritis *[see Warnings and Precautions]*
- Leukocytosis *[see Warnings and Precautions]*
- Capillary Leak Syndrome *[see Warnings and Precautions]*
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis [*see Warnings and Precautions]*

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with igns of maternal toxicity *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.

Data

Human Data

Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neutropenia. Preterm deliveries have been reported in some patients.

Animal Data

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma *[see Clinical Pharmacology and Clinical Studies]*.

Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

OVERDOSAGE

Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions *[see Adverse Reactions]*.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with Fulphila:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome
- Aortitis

Instruct patients who self-administer Fulphila using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

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Real-World Data Underscore the Safety and Highlight the Acceptance of Biosimilar Rituximab

ALTHOUGH NO BIOSIMILAR RITUXIMAB products have become available in the United States—despite the recent approval of Celltrion and Teva's Truxima—biosimilar rituximab products are available in the European Union. Data on their use (published concurrently with the 2019 Annual Meeting of the American Society of Clinical Oncology [ASCO]) highlight not only their safety, but also their growing acceptance among prescribers in Europe.

First, researchers reported interim safety results from a real-world study of Sandoz's biosimilar rituximab, Rixathon, as curative therapy for CD20-positive diffuse large B-cell lymphoma (DLBCL).[1] The study, REFLECT, is the first postapproval real-world study of the biosimilar in DLBCL.

REFLECT includes adult patients with DLBCL who are eligible for treatment with rituximab and cyclophosphamide, doxorubicin, vincristine, or prednisone (R-CHOP). The study's primary end point is complete response rate at the end of treatment.

In an interim analysis, with a cutoff of early September 2018 and with approximately 50% enrollment, the full analysis set comprised 80 patients. In total, adverse events (AEs) were reported in 53 and 13 patients, respectively. There were 19 patients with serious AEs, 2 of which were deemed to be treatment-related. Six AEs led to discontinuation, 6 led to dose interruption, and none led to death.

According to the investigators, these interim data from this ongoing study are as expected for rituximab-based treatment.

Also published alongside the ASCO meeting were data concerning the prescribing of biosimilar rituximab in the European Union.[2]

The study used data from the Ipsos Global Oncology Monitor, which provided deidentified data on 3239 patients with non-Hodgkin lymphoma treated with anticancer drugs in France, Germany, Italy, Spain, and the United Kingdom between July 2017 and September 2018. Data on patients treated with and without a rituximab biosimilar were compared using descriptive statistics.

Although the prescribing of the reference rituximab was stable during the study period, the prescribing of biosimilar rituximab increased significantly, from 7% to 35% (P <.01). The uptake of the biosimilar was particularly strong in Germany and the United Kingdom; by the third quarter of 2018, for those patients who had rituximab prescribed as part of a regimen, prescribing of a biosimilar was 72% in Germany and 63% in the United Kingdom.

Additionally, physicians were more likely in 2018 than in 2017 to state "proven efficacy" and "well tolerated" as their reasons for prescribing the biosimilar.

France, Italy, and Spain had 47%, 32%, and 30% rates of biosimilar prescribing, respectively, which the study suggests may be driven by skepticism about subsequent-entry products that has been observed with generics in some European countries.

Prescribing of the brand name rituximab may also be driven, in part, by the availability of a subcutaneously administered formulation, which is not available for biosimilar versions at this time, the study author noted. ◆

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2. Franceschetti A. NHL and rituximab biosimilar: how have prescribing behaviours changed in EU5 in 15 months? Presented at: American Society of Clinical Oncology Annual Meeting 2019; May 31-June 4, 2019; Chicago, Illinois. Abstract e19054. https://abstracts.asco.org/239/AbstView_239_267249.html.

RESEARCH REPORT

Articles by Jaime Rosenberg

Nivolumab, Ipilimumab Combo Demonstrates Clinical Benefit Among Adults With Pediatric Solid Tumors

THE COMBINATION OF NIVOLUMAB (Opdivo) and ipilimumab (Yervoy) demonstrated significant clinical benefit in patients with solid pediatric tumors that progressed into adulthood—a patient population with few treatment options—according to new study findings.

According to the findings of the first cohort from the phase 2, single-arm study, during a median follow-up of 4.3 months, the combination yielded a 39.3% clinical benefit rate among the 30 patients evaluated.

"Solid pediatric tumors that appear in adulthood are a heterogeneous group characterized by a low incidence, lack of therapeutic options, and reduced survival," wrote the investigators.

While on the treatment, patients achieved a median overall survival of 6.8 months. All patients had locally advanced or metastatic pediatric malignancies that had progressed or were not candidates for traditional therapy.

"One case of metastatic esthesioneuroblastoma achieved a dramatic tumor response and represents the first patient with this extremely rare histology treated with immunotherapy," noted the investigators.

In addition to the 1 patient who achieved a deep partial response during treatment, 10 had stable disease, 17 had progressive disease, and 2 patients died before radiologic evaluation.

The patients, aged 20 to 75 years who were enrolled across 15 centers of the Spanish Group for Rare Cancer, included 4 with medulloblastoma, 4 with neuroblastoma, and 3 with Ewing family tumors. The majority (90%) of patients had received prior systemic therapy, with partial response representing the best response, which occurred in 37% of these patients. The median amount of previous treatment lines was 3.

The treatment regimen consisted of nivolumab 3 mg/kg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks for 6 months or until disease progression or discontinuation due to treatment toxicity, for a maximum of 24 months. Among the 30-person cohort, 6 patients have been treated for at least 6 months, with 1 discontinuing due to adverse events (AEs).

A total of 12 (40%) patients experienced adverse events of any grade and 6 (20%) experienced an AE possibly related to the treatment. ◆

REFERENCE

Mielgo X, Diaz-Beveridge R, Sepulveda JM, et al. Interim analysis of a phase II study of nivolumab combined with ipilimumab in patients with pediatric solid tumors in adulthood (GETHI021). Presented at: American Society of Clinical Oncology 2019 Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract: 2613. https://abstracts.asco.org/239/AbstView_239_251263.html.

Nivolumab, Ipilimumab Combo Yields Clinically Meaningful Responses in Advanced Hepatocellular Carcinoma

NIVOLUMAB (OPDIVO) MONOTHERAPY is currently indicated for the treatment of patients with hepatocellular carcinoma who were previously treated with the targeted therapy sorafenib (sold as Nexavar) based on the CheckMate 040 trial. Assessing the safety and efficacy of nivolumab in combination with ipilimumab (Yervoy) among these patients, investigators have observed clinically meaningful responses and an acceptable safety profile.

These findings showed an overall response rate (ORR) associated with the combination that was double that seen with nivolumab therapy alone. During the CheckMate 040 trial, nivolumab monotherapy yielded an ORR of 14%. These new data on the treatment combination showed an ORR of 31%.

Seven patients achieved a complete response with a median duration of response of 17 months. There was a disease control rate of 49%.

According to the investigators, this is the first report of efficacy and safety for this combination in the patient population.

With a cutoff date of September 25, 2018, the investigators observed a total of 148 patients (treated with sorafenib) randomized to 3 treatment groups:

- Group A: Four doses of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks
- Group B: Four doses of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg once every 3 weeks, each followed by nivolumab 240 mg once every 2 weeks
- Group C: nivolumab 3 mg/kg once every 2 weeks plus ipilimumab 1 mg/kg once every 6 weeks.

Patients were treated until disease progression or intolerable toxicity. At the end of 24 months of follow-up, there was an overall survival (OS) rate of 40%.

Patients in Group A demonstrated the greatest response, with a median OS of 23 months. At 12 months, OS was 61%, and at 24 months, OS was 48%. Sixteen (32%) of the 50 patients achieved any response, with 4 experiencing a complete response and 12 experiencing a partial response. Nine patients experienced disease stability and 20 experienced disease progression.

In Group B, there was a median OS of 12 months among the 49 patients. At 12 months, OS was 56%, and at 24 months, OS was 30%. Fifteen patients achieved any response, with 3 experiencing a complete response and 12 experiencing a partial response. Five patients had disease stability and 24 experienced disease progression.

Median OS among the 49 patients in Group C was 13 months, with a 12-month survival rate of 51% and a 24-month survival rate of 42%. No patients achieved a complete response and 15 patients achieved a partial response; 9 experienced disease stability and 21 experienced disease progression.

Overall, the treatment combination was well tolerated, with 37% of all patients experiencing a grade 3 or 4 treatment-related adverse event. The most common adverse event was pruritus and rash, and 5% of patients had a treatment-related adverse event that led to treatment discontinuation. ◆

REFERENCE

Yau T, Kang YK, Kim TY, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. Presented at: American Society of Clinical Oncology 2019 Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract: 4012. https://abstracts.asco.org/239/AbstView_239_250641.html.

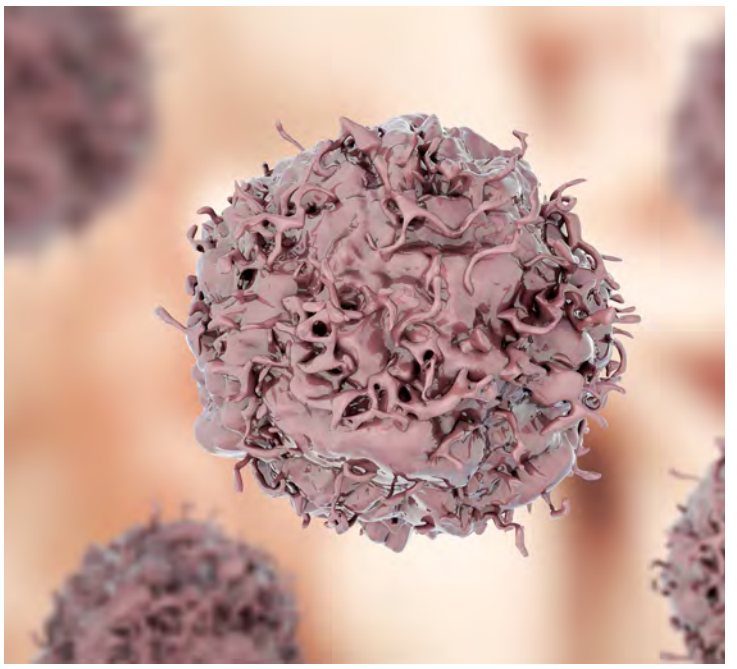
RESEARCH REPORT

Entrectinib Demonstrates Efficacy in Rare Lung Cancer, Pediatric Solid Tumors

A PAIR OF STUDY ABSTRACTS presented at the annual meeting supported the efficacy of entrectinib among 2 different groups of patients, including patients with a rare form of lung cancer and pediatric and adolescent patients with solid tumors.

The first abstract[1] reviewed data coming from 3 phase 1/2 single-arm clinical trials assessing the tyrosine kinase inhibitor entrectinib among 53 patients with *ROS1*-mutated non–small cell lung cancer (NSCLC). Due to the rarity of the tumor type and, therefore, low feasibility of a randomized trial, the investigators identified 69 patients from the Flatiron Health electronic health record–derived database who were treated with crizotinib between January 1, 2011, and June 30, 2018, to compare the efficacy of the 2 drugs. Crizotinib is currently considered standard of care for the patient population.

"In situations where you're dealing with vary rare molecularly defined subpopulations of cancer patients, it's often difficult to conduct a randomized study because of the low feasibility of being able to identify and recruit enough patients," explained Neal J. Meropol, MD, vice president of Research Oncology at Flatiron Health, and an author of the abstract, in an interview with *The American Journal of Managed Care®*. "Given the availability of high-quality, real-world data, there is now the potential to gain insights into the treatment outcomes of patients who are cared for in routine clinical practice, as well as gain a potential comparator to the results of single-arm clinical trials."



A lung cancer cell

MEROPOL

"These results using real-world data support the hypothesis that entrectinib has meaningful activity against lung tumors with *ROS1* fusions and may be superior to current standard of care."

—Neal J. Meropol, MD

Comparing the 2 groups of patients, the researchers observed significantly longer time-to-treatment discontinuation associated with entrectinib compared with crizotinib (14.6 vs 8.8 months). Progression-free survival also favored entrectinib (weighted hazard ratio, 0.44; 95% CI, 0.27-0.74). With a median follow-up of 15.5 months, median overall survival associated with entrectinib was not reached; the weighted median overall survival with crizotinib was 18.5 months.

"These results using real-world data support the hypothesis that entrectinib has meaningful activity against lung tumors with *ROS1* fusions and may be superior to current standard of care. Although provocative, further study is certainly warranted to confirm these results," said Meropol.

The second abstract[2] focused on the use of entrectinib in children aged 4.9 months to adults aged 20 years with recurrent/refractory solid or central nervous system (CNS) tumors. Between May 2016 and October 2018, 29 patients with tumors with mutations in *NTRK1/2/3, ROS1,* or *ALK*, and neuroblastoma (NBL) were enrolled in the study; 28 were evaluated for response.

Among the 6 patients with CNS tumors, 1 achieved a complete response, 3 achieved a partial response, 1 achieved an unconfirmed partial response, and 1 has yet to be evaluated. There were 8 patients with extracranial solid tumors, of whom 6 had a fusion; 1 achieved a complete response and 5 achieved a partial response. Among the 15 patients with NBL, 1 achieved a complete response.

"Entrectinib produced striking, rapid, and durable responses in all children with refractory CNS and solid tumors harboring *NTRK1/2/3, ROS1,* or *ALK* fusions (11 out of 11), as well as in an *ALK*-mutated NBL," wrote the researchers. "No responses were seen in tumors lacking aberrations in target kinases."

Based on the results, the researchers concluded that continued evaluation of entrectinib as a targeted therapy for solid tumors with these fusions, especially in high-grade CNS neoplasms, is warranted. ◆

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RESEARCH REPORT

Articles by Wallace Stephens

Which Predictors Could Identify the Most Costly Patients in Oncology?

COMORBIDITIES, TOXICITIES, AND CERTAIN treatments received, including immunotherapy and bone marrow transplant, were the strongest predictors of high costs among patients with cancer, according to an abstract.

"Quality-based payment programs in medicine are currently being introduced nationally, aimed to improve care and reduce costs," investigators wrote. "This study aimed to evaluate the top spenders [TS] after cancer diagnosis and predict [the] TS at 2 separate time points using predictive analytics."

The investigators collected data about patient characteristics, treatments, adverse events, and outcomes for patients treated for cancer at Mayo Clinic from 2007 to 2017. They obtained standardized costs over a 2-year period after first treatment from Mayo Clinic's Cost Data Warehouse. Medicare reimbursements were assigned to all services and adjusted to the 2017 gross domestic product implicit price deflator for inflation. In the study, TS were identified as patients with costs greater than those in the 93rd percentile, which was $113,158 or higher, due to a substantial rise at that level.

The investigators used descriptive statistics and univariate analysis for comparison. Their prediction model had a training set of 80% and a validation set of 20%, using multivariate selection to predict TS. It was repeated using information available at 2 time points: consultation and last follow-up.

They identified 5626 TS from the 80,385 patients included. The mean overall cost was $44,953. The prediction models had ROC area under the curve statistics of 0.82 at the first time point and 0.89 at the second time point in the training set and 0.82 and 0.88, respectively, in the validation set, which indicated good prediction of high costs.

The investigators found these factors to be the most predictive of TS:

- Blood transfusions within 90 days of treatment (odds ratio [OR], 5.3)
- Bone marrow transplant (OR, 4.0)
- Mild liver disease (OR, 3.5)
- Hemiplegia, with an (OR, 3.4)
- Weight loss above 10% within 90 days of treatment, with an (OR, 3.3)
- Upper gastrointestinal cancer (OR, 3.0)
- "Other" cancer type (OR, 2.8)
- Immunotherapy (OR, 2.7)
- Hospitalizations within 90 days (OR, 2.4)

The investigators also found the highest costs resulted from hospital services in the TS and non-TS groups. The mean costs of hospital services were $114,258 and $13,185, respectively.

"This is the first study to predict with high accuracy the top spenders in oncology," they wrote. "Our findings suggest that quality payment programs should adjust for comorbidities and that reducing toxicity may be an effective method at reducing costs." ◆

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What Affects Time to Diagnosis in Children, Adolescents, and Young Adults With Solid Tumors?

TIME TO DIAGNOSIS AMONG CHILDREN, adolescents, and young adults (AYAs) varies by cancer type and may be affected by clinical and sociodemographic factors, according to an abstract.

Investigators used claims data for commercially insured enrollees in a large United States health plan from OptumLabs' data. They identified pediatric patients 14 years and younger and AYAs aged 15 to 39 years with soft tissue sarcomas (STS), bone tumors (BTs), and germ cell tumors (GCTs) diagnosed between 2001 and 2017 who were continuously enrolled for 6 months prior to their diagnosis.

Time to diagnosis was calculated as the number of days between a patient's first medical encounter associated with a potential cancer symptom and their diagnosis date. The researchers compared median times from first symptom to diagnosis using the Wilcoxon Rank Sum Test. They used multivariable logistic regression to identify sociodemographic and clinical factors associated with intervals longer than 3 months from appearance of symptoms to diagnosis.

Of 11,395 total patients, 86% presented to medical care with symptoms before their diagnosis. A total of 2228 patients had STS, 1565 patients had BTs, and 5904 had GCTs. The most common symptoms reported were pain and swelling. The researchers found that GCTs had the shortest median time to diagnosis (49 days), followed by BTs (91 days) and STS (92 days).

There was a significant difference in median days to diagnosis by age:

- For patients with BTs, the median times to diagnosis was 69 days for those 14 years or younger, 77 days for patients aged 15 to 21 years, and 105 days for patients aged 22 to 39 years.
- For patients with GCTs, the median times to diagnosis was 96, 34, and 49 days, respectively.

There was not a significant difference in median days to diagnosis by age for STS.

The investigators also found that being from a household with a college degree or higher level of education, as well as seeing a specialist other than an oncologist when symptoms first appeared, was associated with a longer delay in diagnosis. Older age and being male were associated with a shorter delay in diagnosis.

"In a commercially insured population, time to diagnosis varies by cancer type and is impacted by clinical and sociodemographic factors," the investigators wrote. "Shorter time to diagnosis may represent delays in presenting to medical care or more acute presentations of symptoms. Therefore patient-reported symptoms and barriers to care data should be collected to better define strategies to reduce delays in diagnosis." ◆

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Alvarez EM, Winestone L, McPheeters J, et al. Factors impacting time to diagnosis in pediatric, adolescent and young adult (AYA) patients with solid tumors. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract e21515. ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.e21515.

RESEARCH REPORT

Can Nivolumab Effectively Treat Metastatic RCC When Resources Are Limited?

NIVOLUMAB (OPDIVO) IMMUNOTHERAPY could effectively treat metastatic renal cell carcinoma (mRCC) in resource-constrained settings when the intervals between dosages are longer and when treatment is cut short for patients who respond, according to an abstract presented at the annual meeting.

"Nivolumab is now a standard second-line treatment for patients [with] mRCC who progress on first-line sunitinib or pazopanib," the investigators wrote. "Most Western centers use nivolumab for either 2 years duration, or indefinitely, or [until] severe side effects. Due to high drug cost and lack of insurance, it is difficult for most of our Indian patients to afford this duration of treatment. So, we decided to study the impact of increasing intervals between standard doses of nivolumab and stopping treatment early in responding patients [with] mRCC."

The investigators onducted a single-center, retrospective study of patients with mRCC. Twenty-eight patients were treated with nivolumab between May 2016 and December 2018. Twenty-four patients initially received oral tyrosine kinase inhibitors (TKIs):

- 13 received sunitinib
- 10 received pazopanib
- 1 received sorafenib

The 4 patients who were not initially given TKIs received nivolumab as first-line therapy: 2 as a single agent and 2 with oral TKIs.

Participants received either 3 mg/kg or 240 mg of nivolumab every 2 weeks for 6 initial cycles. The time between cycles was extended to 3 weeks if patients had a complete response (CR), a partial response (PR), or stable disease (SD). The doses were extended to 4 weekly intervals after 9 months. The study's end points were objective response rate (ORR), overall survival (OS), and adverse events.

Patient response was assessed by Response Evaluation Criteria in Solid Tumors. The investigators found:

- 3 (10.7%) patients achieved a CR
- 7 (25.0%) patients achieved a PR
- 7 (25.0%) patients had SD
- 11 (39.2%) patients had progressive disease

Treatment was halted after 18 doses for the 3 patients who achieved a CR. The duration of follow-up after treatment ended ranged from 8 to 18 months. The 3 patients who achieved a CR remained in CR. Of the 3 patients with SD, 1 received 22 cycles and 2 received 19 cycles. The OS at 1 year was 60%. The median OS was not reached.

"An ORR of 36% and OS at 1 year of 60% is the best we have seen. Long-lasting responses, even after discontinuing therapy, have been seen. This enables us to reduce the cost of treatment without possibly losing efficacy, and this could be an important step forward for treating more patients with nivolumab in our resource-constraint setting," the researchers concluded. ◆

REFERENCE

Rauthan A, Patil P, Yashas N, et al. Immunotherapy with nivolumab in metastatic renal cell carcinoma in resource constraint settings: impact of increasing intervals between standard doses, and stopping treatment early in responding patients. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract e16078. ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.e16078?af=R.

Laura Joszt, Jaime Rosenberg

Removing Barriers to Improve the Use of Diagnostic Tests for Precision Cancer Care

CURRENTLY, THE NUMBER of patients who are actually utilizing precision cancer care treatments is small, but it is growing fast. As that happens, physicians will need to get comfortable with ordering the right tests, explained Clynt Taylor, chief executive officer of Intervention Insights, and Lee Newcomer, MD, formerly of UnitedHealth Group.

There are, according to Newcomer, 3 big barriers to getting access to diagnostic tests and wider adoption of precision medicines. First is the challenge of figuring out what panel the clinician needs to order. Do they need to order a single-gene or a 7-gene or even a 500-gene panel?

"So, that clinical question is pretty tough for physicians to answer right now," he said. "All of this is new. It's evolving. They struggle with it."

A second barrier is choosing the laboratory that offers the best test for what the physician needs. The third barrier is figuring out which tests are covered by the payer. There is a lot of work on the part of the physician to get through all 3 of those barriers, involving multiple phone calls.

Newcomer is now on the board of Intervention Insights, which has a product, Trapelo, that tries to remove some of those barriers. According to Taylor, there is wide variability in oncologist level of comfort with using precision medicines, which is another barrier that Trapelo tries to overcome.

Intervention Insights had started in the area by developing a knowledge base of all evidence related to genes or biomarkers and their diseases. That information was used to provide a summary for reports coming back from the lab to make it easier for physicians to interpret the results, Taylor explained. Trapelo is the next step and moves downstream a little to help physicians start making decisions around which tests to order.

After working with physicians, the company decided that a single platform could help align the interests of oncologists, laboratories, and payers in real time, "so that our colleagues could look to order from a single place that would help that doctor know, for each patient, what to order, from which labs, what genes needed to be tested, [and] what would be paid for them," Taylor said.

This work takes place in the electronic medical record (EMR), and according to Taylor, the company was very aware that Trapelo needed to work very synergistically with the EMR so as not to add more work to the day for oncologists. The usability of the program was key, Newcomer added.

For a while now, the diagnostics field has been tough to reimburse because of the Current Procedural Terminology codes used, Newcomer said. These codes have been nondescript and confusing, and health plans have been looking for vendors who can make it easier to understand what test is being ordered and how to pay for it.

New payment models, such as the Oncology Care Model (OCM), help to get diagnostic tests used more, because OCM rewards practices that are cost-efficient and get better outcomes.

"So, if you were to know in advance from the gene test, that drug probably isn't going to work, whereas another one will, that's very useful information…" Newcomer said. ◆

Despite Growth, Uptake of Downside Risk in ACO Contracts Remains Low

ALTHOUGH THE NUMBER OF accountable care organization (ACO) contracts with downside risk is growing, the majority of ACOs remain in upside-only risk contracts, according to a new study. In 2012, 28% of accountable care organizations (ACOs) had a contract with downside risk. That rate increased modestly to 33% in 2018.

However, according to study researchers, the number of ACOs has increased approximately 5-fold during the time period, which could mean that the number of ACO downside risk contracts also grew significantly.

Although the increase in the amount of ACOs taking on downside risk remains modest, there has been significant growth in not just the number but also the variety of contracts implemented by ACOs, including in the number of payers they contract with. In 2012, 42% of newly formed ACOs had contracts with 2 or more payer types compared with 63% of ACOs in 2018.

As ACOs have emerged as one of the most broadly implemented value-based payment models, CMS has been pushing ACOs to take on more financial risk. In December 2018, the agency finalized Pathways to Success, its overhaul of the Medicare Shared Savings Program, which will push ACOs to assume risk more quickly. Notably, the program replaced the traditional 3 tracks with 2 new tracks in which ACOs will start in a 1-sided model and incrementally phase in higher levels of risk. Down from the current 6 years, ACOs will be able to stay in 1-sided risk for 2 years and existing ACOs will be able to stay for 1 more year.

The researchers of the new study, published in Health Affairs, drew on data from the National Survey of Accountable Care Organizations, finding that ACOs taking on downside risk were more likely to have more experience with other forms of risk-bearing contracts.

"Prior work indicates that ACO participants with risk-bearing experience are more likely to achieve shared savings with the Medicare program," wrote the researchers. "Therefore, the assumption that inducing more ACOs to bear downside risk would result in increased savings should be questioned, based on what is known to date."

Among the 419 ACOs that completed the survey in 2018, those assuming downside risk were less likely to be physician led (43% vs 57%) and instead more likely to be jointly led by a hospital and physicians, led by a hospital, or led by another arrangement, including coalitions and regional, county, or state organizations. They were also less likely to be physician owned than other ACOs were (30% vs 39%).

"While similar in proportion of ownership by hospitals, downside-risk ACOs were more likely than other ACOs to be owned by other entities, including public ownership, non-profit ownership, or another privately owned for-profit entity," reported the researchers.

The survey results also indicated that ACOs taking on downside risk were more likely to:

- Be integrated delivery systems (58% vs 42%) and include a hospital and have a greater number of hospitals
- Directly provide or contract to deliver inpatient rehabilitation, routine specialty care, palliative or hospice care, home health or visiting nurse services, and skilled nursing facility care
- Report that 50% to 100% of their primary care patients were covered by an ACO contract ◆

REFERENCE

1. Peck K, Usadi B, Mainor A, Fisher E, Colla C. ACO contracts with downside financial risk growing, but still remain in the minority [published online July 1, 2019]. *Health Aff* (Millwood). doi: 10.1377/hlthaff.2018.05386.

Jaime Rosenberg, Mary Caffrey, Allison Inserro, Samantha DiGrande

13 Years After the HPV Vaccine Was Introduced, US Uptake Remains Low

PARTH SHAH, PHARMD, PHD, of the Fred Hutchinson Cancer Research Center, led a session to discuss the uptake challenges of the human papilloma virus (HPV) vaccine at the 2019 Annual Meeting of the American Society of Clinical Oncology. He began by explaining the known percentages of cancers attributable to the virus in the United States: cervical cancer, 91%; vagina cancer, 75%; and vulva cancer, 69%, among others.

Although multiple cancers are attributable to the virus, explained Shah, of the ages in the United States that should be vaccinated—13 to 17 years—both boys and girls, only 49% receive the vaccine.

The challenges around facilitating larger uptake of a vaccine that prevents cancer can be frustrating for providers. Parents' hesitancy about the HPV vaccine has been around since it was approved in 2006, although it has garnered more attention as the antivaxxer movement has taken hold in the United States, as seen by the 1044 confirmed cases of measles this year. (This is the greatest number of cases reported in the United States since 1994, and since the disease was declared eradicated in 2000.)

In terms of the low uptake of the HPV vaccine, Shah believes the reasons are multifactorial. Namely, low uptake can be attributed to societal and cultural norms, community, and relational and individual reasons.

"As far as societal reasons, a few states currently have [initiated] or tried to initiate school mandates for the vaccination," he said. "Not only were they controversial, but they were largely ineffective. When the vaccine came out and school mandates were being discussed, it was largely pushed by the manufacturers, which generated distrust. In terms of community challenges, we're vaccinating in some schools, but schools are governed by local jurisdictions and sometimes providing preventive services is not a priority. And finally, for relational and individual reasons, you need to consider the parents' perspective."

Shah explained that over the past few years, the CDC has collected data on why parents choose to not vaccinate their child for HPV. Top reported reasons include safety concerns, adverse effects, lack of knowledge about the vaccine, not believing it was necessary, and no provider recommendation. Parents also reported that their child was not sexually active, so they did not need it.

Based on prior data and studies, Shah recommended that when speaking with patients who are due for the vaccine and their parents, the physician should make a statement that notes the child's age, announce that they are due for vaccines that prevent several diseases, place the HPV vaccine in the middle of the list, and say that you're available to vaccinate today.

Deanna Teoh, MD, MS, FACOG, FACS, of the University of Minnesota, emphasized the impact of social media on vaccination trends. The younger population is more likely to receive their news from social media, while Facebook is the site where adults get most of their news. Multiple social media sites—Facebook, YouTube, Twitter, and more—have been in hot water recently for providing a space for the antivaxxer movement to gain strength. Oversight of inconsistent site governance policies has been attempted since the rise of the measles outbreak.

To offer a different perspective, Ian Frazer, MBBS, MD, DSc, of the University of Queensland in Australia, explained that uptake of the vaccination is not a problem in Australia, in part because "we bribe them to get vaccinated. There is a substantial social security handout if your child is fully vaccinated by 5 years old, so we find that most countrywide vaccination rates are high."

Frazer and his late colleague, Jian Zhou, PhD, developed and patented the basic technology behind the vaccine.

Because most Australians saw the vaccine as a local invention, Frazer explained that uptake was quite good. In fact, the question being asked now in Australia is should it continue with screening for the disease since the vaccination rates are so high.

However, the question is not as straightforward as it seems, because the only screening tool available for HPV is a Papanicolaou (Pap) smear. This presents a problem, as only females, or roughly half the population, can be screened.

An audience member brought the room's attention to another problem in regard to lack of knowledge about the importance of the vaccine not previously mentioned: "Some patients truly don't even know that they have an HPV-related cancer. We need to first educate patients about their own disease and then address the fact that there's a vaccine to prevent it," she said. This way, they'll share that information with their loved ones and maybe a greater uptake will start to occur. ◆

REFERENCE

Measles cases in 2019. CDC website. cdc.gov/measles/cases-outbreaks.html. Updated June 10, 2019. Accessed June 1, 2019.

Exploring Oncology Financial Toxicity, Cost of Care

TWO POSTERS PRESENTED at the 2019 Annual Meeting of the American Society of Clinical Oncology discussed the growing issue of financial toxicity and the costs of care in cancer treatment.

In the first poster, researchers selected 4 phase 3 trials of immuno-oncology (IO) treatments for non-small cell lung cancer (NSCLC) in a first-line setting and found that while median progression-free survival has doubled, so did costs. The researchers said the expense has to be quantified in relation to per capita gross national product in the United States ($53,128 in 2017). Costs appear economically unsustainable even when accepting a higher threshold of $100,000 for 1 quality adjusted life year gained, they wrote. But given the significant PFS gains, there is a need to use IOs through innovative cost sharing platforms, they said.[1]

In the second poster, researchers hypothesized that weight-based dosing of pembrolizumab and nivolumab in order to allow vial sharing among patients would result in substantial cost savings.[2] The 2 drugs were originally investigated and FDA-approved with weight-based dosing strategies, but later the approval label was amended to a fixed-dose administration.

Researchers retrospectively examined all outpatient doses of pembrolizumab and nivolumab given at 3 Stanford Medicine infusion centers between July 1, 2018, and October 31, 2018, using the Stanford Medicine Research Data Repository (STARR) database. Cost-minimization analysis was conducted to model the impact of dosing strategies based upon patient weight versus fixed dosing (2 mg/kg vs 200 mg every 3 weeks for pembrolizumab; 3 mg/kg vs 240 mg every 2 weeks or 6 mg/kg vs 480 every 4 weeks for nivolumab).

"Dose-minimization" (DM) was defined as whichever dose was lower (weight-based or fixed dose). The impact of allowing vial sharing (considering commercially available vial sizes) between patients treated at the same site and on the same date was assessed. Average sales price from CMS for Part B drugs was used for cost estimates.

A total of 1029 doses of pembrolizumab or nivolumab were administered across a variety of cancer types. For most doses (n = 789, 77%), the calculated weight-based dose was less than the fixed dose. DM resulted in decreased usage and expenditures of both pembrolizumab and nivolumab, and a further decrease was observed with vial sharing.

Total savings estimated with DM and vial sharing strategy were greater than $1.4 million. This amounted to savings of >22,000 mg of pembrolizumab (112 fixed doses) and >11,000 mg of nivolumab (47 fixed doses). Savings were greatest at the highest volume infusion center.

Alternative dosing strategies of pembrolizumab and nivolumab would result in significantly less drug utilization and pharmaceutical spending, without anticipated impact on efficacy, but there are barriers to this approach, such as existing policies regarding vial sharing and drug vial sizes. ◆

REFERENCES

1. Ashraf SMM, Pandita S, Alimpertis E, et al. Progression free survival (PFS) benefits of immuno-oncology agents (IOs) and implications for market cost-sharing inefficiencies. Presented at: American Society of Clinical Oncology Annual Meeting, May 31-June 4, 2019; Chicago, Illinois. Poster 334.
2. Hall ET, Zhang J, Kim EJ, Economic analysis of alternative pembrolizumab and nivolumab dosing strategies at an academic cancer center. Presented at: American Society of Clinical Oncology Annual Meeting, May 31-June 4, 2019; Chicago, Illinois. Abstract 6504.

Effective April 1, 2019, the following C-code can be used for administrative and billing purposes specific to LIBTAYO® (cemiplimab-rwlc):

LIBTAYO®
(cemiplimab-rwlc)
Injection 350 mg

C9044, INJECTION, cemiplimab-rwlc, 1 mg, for hospital outpatient use

For dates of service prior to **April 1, 2019**, use the appropriate unspecified HCPCS C-code (C9399 for unclassified drugs or biologics) to bill for LIBTAYO.

How supplied[1]

LIBTAYO is supplied in a carton containing 1 single-dose vial of 350 mg/7 mL (50 mg/mL).

Recommended dosage[1]

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Strength[1]
350 mg/7 mL (50 mg/mL)
NDC[1]
61755-008-01

The Centers for Medicare & Medicaid Services assigned a 1 mg billing unit for LIBTAYO (1 mg of LIBTAYO = 1 unit). Coding requirements may vary by payer; please verify coding requirements before submitting claims.

Indication

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%), and Grade 2 (1.3%). Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg/day or equivalent. Pneumonitis resolved in 62% of patients. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated colitis: Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%). Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg/day or equivalent. Colitis resolved in 80% of patients. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%). Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg/day or equivalent. Hepatitis resolved in 64% of patients. Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

(Continued)

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

Important Safety Information

Warnings and Precautions (continued)

Immune-mediated endocrinopathies: Withhold LIBTAYO if clinically necessary for Grade 2, 3, or 4.

- **Adrenal insufficiency:** Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.2%)
- **Hypophysitis:** Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of 1 patient with Grade 3 hypophysitis
- **Hypothyroidism:** Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%); no patients discontinued hormone replacement therapy
- **Hyperthyroidism:** Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%); hyperthyroidism resolved in 38% of patients
- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%); type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients

Immune-mediated nephritis with renal dysfunction: Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%). Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg/day or equivalent. Nephritis resolved in all patients. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated dermatologic adverse reactions: Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%). In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥40 mg/day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO or were reported with the use of other PD-1–blocking and PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. Withhold LIBTAYO for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy
- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis
- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia rheumatica
- **Hematological and immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse reactions

- Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in ≥2% of patients were cellulitis, sepsis, pneumonia, pneumonitis, and urinary tract infection. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue
- LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness
- The most common adverse reactions (incidence ≥20%) were fatigue, rash, and diarrhea

Use in specific populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see accompanying Brief Summary of Prescribing Information on the following pages.

Reference: LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PD-1=programmed death receptor-1; NDC=National Drug Code.

REGENERON | SANOFI GENZYME

LIBTAYO® (cemiplimab-rwlc)
Injection 350 mg

LIBTAYO® (cemiplimab-rwlc) Injection 350 mg

LIBTAYO® (cemiplimab-rwlc) injections, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.2 Dosage Modifications for Adverse Reactions

Withhold or discontinue LIBTAYO to manage adverse reactions as described in Table 1. No dose reduction of LIBTAYO is recommended.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	LIBTAYO Dosage Modifications
Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN.	Withhold†
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, or 4	Withhold if clinically necessary
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold†
	Grade 4	Permanently discontinue
Recurrent or persistent immune mediated adverse reactions	• Recurrent Grade 3 or 4 • Grade 2 or 3 persistent for 12 weeks or longer after last LIBTAYO dose • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last LIBTAYO dose	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

*Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

2.3 Preparation and Administration

- Visually inspect for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

Preparation

- Do not shake.
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

Storage and Infusion Solution

- Store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

Administration

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not be inclusive of all possible immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions *[see Dosage and Administration (2.2)]*. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over one month *[see Dosage and Administration (2.2)]*. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%) and Grade 2 (1.3%) *[see Adverse Reactions (6.1)]*. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

Immune-Mediated Colitis

Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%) *[see Adverse Reactions (6.1)]*. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 60% who received prednisone ≥40 mg per day or equivalent. Colitis resolved in 80% of patients.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%) *[see Adverse Reactions (6.1)]*. Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥40 mg per day or equivalent. Hepatitis resolved in 64% of patients.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), and Grade 2 (0.2%) *[see Adverse Reactions (6.1)]*.

Hypophysitis

Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one patient with Grade 3 hypophysitis.

Hypothyroidism

Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%). No patients discontinued hormone replacement therapy.

Hyperthyroidism

Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Hyperthyroidism resolved in 38% of patients.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%) *[see Adverse Reactions (6.1)]*. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥40 mg per day or equivalent. Nephritis resolved in all patients.

Immune-Mediated Dermatologic Adverse Reactions

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) *[see Adverse Reactions (6.1)]*. In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥40 mg per day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 534 patients who received LIBTAYO *[see Adverse Reactions (6.1)]* or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Neurological: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Cardiovascular: Myocarditis, pericarditis, vasculitides

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a VogtKoyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis

Musculoskeletal and Connective Tissue: Myositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Hematological and Immunological: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.2% of patients receiving LIBTAYO *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction *[see Dosage and Administration (2.2)]*.

5.3 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to LIBTAYO in 534 patients in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 98 patients with metastatic (nodal or distant) CSCC, 65 patients with locally advanced CSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=446), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=6), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=23). Among the 534 patients, 38% were exposed for ≥6 months and 16% were exposed for ≥12 months.

The data described below reflect exposure to LIBTAYO in 163 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=139) or 350 mg every 3 weeks (n=23) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 20 weeks (3 days to 1.4 years).

The safety population characteristics were: median age of 71 years (38 to 96 years), 85% male, 96% white, and ECOG performance score (PS) of 0 (44%) or 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash and diarrhea. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness. Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients and Table 3 summarizes Grade 3 and 4 laboratory abnormalities worsening from baseline in ≥1% of patients receiving LIBTAYO.

Table 2: Adverse Reactions in ≥10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	LIBTAYO N=163	
	All Grades %	Grade 3-4 %
Skin and Subcutaneous Tissue		
Rash*	25	1.2
Pruritus†	15	0
Gastrointestinal		
Diarrhea‡	22	0.6
Nausea	19	0
Constipation	12	0.6
General and Administration Site		
Fatigue§	29	2
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	17	3
Metabolism and Nutrition		
Decreased appetite	10	0

*Rash is a composite term that includes rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction.
†Pruritus is a composite term that includes pruritus and pruritus allergic.
‡Diarrhea is a composite term that inlcudes diarrhea and colitis.
§Fatigue is a composite term that includes fatigue and asthenia.
#Musculoskeletal pain is a composite term that includes: musculoskeletal pain, back pain, myalgia, neck pain, pain in extremity.

Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Laboratory Abnormality	Grade 3-4 (%)†
Chemistry	
Increased aspartate aminotransferase	3
Increased INR	2
Hypoalbuminemia	1
Hematology	
Lymphopenia	7
Anemia	2
Electrolytes	
Hypophosphatemia	4
Hyponatremia	3
Hypercalcemia	1

†Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 398 of 534 patients who received LIBTAYO and the incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.3% using an electrochemiluminescent (ECL) bridging immunoassay; 0.3% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death *(see Data)*. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO *[see Use in Specific Populations (8.1)]*.

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following *[see Warnings and Precautions (5.1)]*:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.
- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that LIBTAYO can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of LIBTAYO *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

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Edited for clarity.

Michael J. Birrer, MD, PhD, Director, O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham

How well is oncology research being integrated into clinical management of patients? How can it be done better?

Well, [in] my long, illustrious experience in oncology, I've sort of seen it all, and I think that in the late '70s, '80s, and I'll even go into the '90s, so much of oncology development was empirical. We would take drugs off the shelf that essentially had been shown to damage DNA or showed some cytotoxic effects against the tumor cells and then we would bring that in an empiric way into the clinic. I think that sort-of almost unscientific approach explained at that time why things moved so slowly.

Why were we stuck on carboplatinum-taxol for ovarian cancer for so long? Because we were doing this, yet another cytotoxic agent from off the shelf, from the lab, into the clinic. That's completely changed, and to answer the question directly, I think we're bringing laboratory discoveries into the clinic in a much more efficient and rational way than we ever have in oncology. What I've seen change in the last 5 or 10 years has been just astonishing. And there's multiple advantages of this. So first of all, the transit time is quick. Whereas it used to take 20 years to develop a drug, we've now had some drugs approved in the phase 1 setting. That's certainly true in lung cancer.

So, I can't say that we've gotten it down to 3 to 5 years, but we probably are developing drugs effectively under the 10-year limit, which is half of what it used to be.

The second issue, [which is] really important for patients, and I tell my patients this, the science is so robust that when the drug gets into the phase 1 [trial], you now have a drug for which the chance of a success is high, the chance of efficacy is higher, and the chance of toxicity is lower. So, I used to have an old adage. I'd tell my patients that I would never recommend them go for a phase 1 trial if it was outside of a 50-mile radius because traveling all that distance for something that was unlikely to work and maybe toxic wasn't worth it. It's completely changed now.... Now I have patients fly in for a phase 1 trial because it's a novel combination, because there's a lot of really interesting science behind it, and its chance of being successful is much higher than it was 10 or 15 years ago.

Catherine M. Diefenbach, MD, Hematologist–Oncologist, NYU Langone Health

Can you discuss the importance of reducing toxicity in the treatment of lymphoma? How does this affect patients' overall health, in addition to quality of life?

I think in general, it's really important to use the new drugs that we're discovering that are targeted and to combine them intelligently with standard chemotherapy. Because we know that intensive chemotherapy regimens, while very effective in the first line for patients who have [a] short response or refractory disease, are generally not effective in later lines, unless you go to really high doses. And most patients don't tolerate this well, especially if they're older or if they have significant toxicity. So, trying to take existing chemotherapy at lower doses and combine it with targeted strategies or immunotherapy is a way to both circumvent the higher toxicity of cytotoxic chemotherapy and rely on tumor biology to be smarter, rather than more aggressive, about targeting lymphoma.

Roy S. Herbst, MD, PhD, Chief of Medical Oncology, Yale Cancer Center

There is a lot of research into predictive biomarkers in cancer. How well is that research making it into practices and actually being used with patients who can benefit?

It's incredible what's happened now with personalized therapy of cancer. Targeted therapy for lung cancer, we now have 8 or 9 different markers, which if you have them, different oncogenes can allow a physician to give their patient a targeted drug, which might have a response rate upwards of 50% with much less toxicity than chemotherapy.

These are being used, [but] the problem is some of the drivers are rather new, such as *RET*, *NTRK*, *MET*, and we're still not in all places screening patients for these markers. So it's going to be very important that people watching this, whether patients or physicians, ask, "Is the profiling test that's being done at your center or your hospital, that you're getting as a patient, including all the newest drivers for lung cancer?" Because only if you look for them can you then try to find the therapy either in your local providers office, or if not, since some of these agents are still rather new, there are clinical trials running at many sites.

The nice thing about 2019 is clinical trials really occur almost every place in the United States. So, these things are beginning to get into common practice. At my institution at Yale, we have a center in downtown New Haven, we have 12 to 13 sites around Connecticut, we're making sure everyone uses the profiling system.

And then there have to be discussions. And things like this [interview] will help people to discuss and learn and understand the importance of these new markers and how to match for the right drug.

Andrew H. Ko, MD, Colorectal and Gastrointestinal Cancer Specialist, University of California San Francisco

You helped write the National Comprehensive Cancer Network (NCCN) Guidelines Insights for pancreatic adenocarcinoma. What was the treatment recommendation for these patients?

NCCN guidelines are a panel of experts in a particular field who gather together to analyze data and interpret them to help guide recommendations for how we manage and treat patients with a particular disease. I'm on the guidelines panel for pancreatic cancer. So, again, some of the

specifics in terms of choices of chemotherapy and uses in the advanced or metastatic setting or the adjuvant setting, those are based—as much as possible—usually on randomized data.

In terms of the latest updates, I think probably the most impactful one is the importance of at least considering genetic testing [in] all patients.

In the past, we used to be a little bit selective in whom we would recommend that for, but now it's almost a universal recommendation that we at least consider doing genetic testing. By that I mean, even if someone doesn't have a provocative family history of cancer, we should think about doing genetic testing on those individuals to see if they have any hereditary susceptibility genes.

The classic one would be someone [who] has a germline *BRCA,* either *BRCA1* or especially *BRCA2,* mutation because not only does that have particular implications for screening family members, but now we know that it actually has very substantive therapeutic implications for the patients themselves, with the use of PARP inhibitors and a greater sensitivity to platinum agents, for example.

I think that's a very important piece that perhaps goes underrecognized still in the community, and that's a little different from just tumor-based molecular testing, which also, actually we believe, should be done or at least be thought of on a more consistent basis. And that's basically looking at any mutations or genetic alterations within the tumor itself, so sematic mutations or genetic changes, because what I usually tell patients is any information is good to have. It's not always actionable, but if we happen to find the patient who has evidence of microsatellite instability, or an NTRK fusion, well we have very specific treatments for those situations, and we have clinical trials available sometimes for patients with other mutations [who] are selected for those specific mutations. So I think doing that as much as possible, doing that kind of molecular profiling, is also something that should be considered routinely.

Despite there being a growing number of therapeutic options for pancreatic cancer, a recent study found one-third of these patients don't see a medical oncologist and more don't receive treatment. Why do you think that's the case? Can anything be done to improve those numbers?

I think pancreas cancer, because it's historically been felt to be a pretty dismal disease in terms of prognosis and patients faring poorly, I think there's perhaps been a sometimes-nihilistic philosophy that some providers even still have despite our growing array of options for patients. So, I think part of it is that education piece for providers, but also for patients and families themselves. I think aggressive symptom management—because sometimes when a patient presents, the thought is, "Well, they're not a candidate for treatment because they have such severe pain or because they're losing so much weight"—if we can aggressively manage those cancer-related symptoms, it may afford the opportunity to at least offer them some treatments. We recognize that our current treatments may help some individuals a lot, some maybe just a little, and some not at all, but I think just giving them that opportunity, if they're well enough, to even try…I always want that option to be available to patients, and I think that's perhaps one of the main challenges specific to pancreatic cancer.

David Ortiz, Oncology Care Model Program Director, Montefiore Einstein Center for Cancer Care

With all the changes being made to practices under the Oncology Care Model (OCM), are there any specific things where you've seen the biggest return on investment?

I think it's given us justification to reamplify an old argument. So, cancer centers and cancer programs need to have an urgent arm or an urgent care arm—something to mediate those patients that are in turmoil or in crisis or microcrisis. They're just starting chemotherapy and they're feeling crappy. What do you do?

There needs to be that outlet. Someone that can answer those questions and tell them, "You know what, it's perfectly normal. This is fine." Or "that's out of the ordinary, out of the range. I think you should come see me now." OCM has given us the opportunity to re-engage and thankfully, we're moving in that direction.

Do you see OCM as being the future of cancer care, or is it just a step onto another model?

I think OCM in the microcosm is exactly what we should look to expect in every other future iteration. I think it expands to other payers. We're looking to do that with organizations that have had success doing that and we want to emulate that.

I think that we are clearly finding that there is a benefit for the patient, and there is clearly a benefit to the organization, because we're keeping the patient connected to the care. They're more adherent, they're more able to escalate an issue and not just drown by themselves. I think doctors also know that if there is someone who needs help there is a navigator who should be in place to try to help that individual. So, there's mechanisms on both ends—for the clinicians and for the patients. So, I think it is the future. ◆

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