More **Innovation** Is on Tap for 2021

*Five Experts Describe Key Trends*

Howard A. “Skip” Burris III, MD, on Drug Development
Debu Tripathy, MD, on **BREAST TUMORS**
Balazs Halmos, MD, MS, on **LUNG CANCER**
Neeraj Agarwal, MD, on **GU MALIGNANCIES**
Lori A. Leslie, MD, on **Hematologic Cancers**

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**PEER EXCHANGE**

**GI MALIGNANCIES**
Recent Data Drive New Gastric, GE Strategies

**OnePathways**
MLL Fusion Proteins Emerge as AML Target

**HEMATOLOGIC MALIGNANCIES**
ASH 2020 Highlights

**GENITOUREINARY CANCER**
Frontline Planning Undergoes Changes in Metastatic RCC
*By Juan Javier-DesLoges, MD, MS; Ithaar Derweesh, MD; and Rana R. McKay, MD*

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**VANDERBILT-INGRAM CANCER CENTER**
Adult Nonmalignant Hematology Is an Endangered Field That Merits Protection
*By Jennifer R. Green, MD*
ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too¹²

With each relapse, multiple myeloma becomes increasingly difficult to control. As the disease progresses, very few patients (less than 5%) experience a deep response.¹² However, evidence suggests a deep response may be associated with improved PFS and OS.¹³ Therefore, shouldn't a goal of treatment be to achieve a deep response in as many patients as possible?

The hope is that more patients may achieve a deep response with emerging therapies on the horizon.

Learn more about why depth of response matters in relapsed or refractory multiple myeloma.

Visit ThinkDeepMM.com

OS=overall survival; PFS=progression-free survival.

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 60.
IN HER2+ EARLY BREAST CANCER (EBC), UNDERSTAND HER RISK OF RECURRENCE
HER RISK OF RECURRENCE REMAINS, EVEN AFTER NEOADJUVANT TREATMENT

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery.\textsuperscript{1,2}

The CTNeoBC pooled-analysis assessed the risk of recurrence following neoadjuvant treatment among patients with breast cancer, including HER2+ EBC, based on historic data\textsuperscript{1}

The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease.\textsuperscript{1}

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes.\textsuperscript{1}
The pooled-analysis showed that patients were still at risk of recurrence following neoadjuvant therapy, even if a pathological complete response (pCR) was achieved; and the risk of recurrence was even higher for those with residual invasive disease. 1

This analysis included 12 international trials published between January 1, 1990, and August 1, 2001, assessing neoadjuvant treatment in patients with various breast cancer subtypes. 1

Your patients with HER2+ EBC are still at risk of recurrence, regardless of the outcome of neoadjuvant treatment and surgery. 1,2

Association between pCR and event-free survival (EFS)* in the HER2+ subgroup analysis of the CTNeoBC study1

*EFS was calculated as the interval from randomization to occurrence of disease progression resulting in inoperability, loco-regional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause.1

1,989 patients with HER2+ tumors were included in the subgroup analysis. 55% of which did not receive a full year of adjuvant HER2-targeted monotherapy treatment.1

While there are different paths you can choose for your patient with HER2+ EBC, her treatment shouldn’t stop at neoadjuvant therapy.
Discover possible adjuvant treatment options that may be right for her*:

For patients who achieve pCR, visit PCRinEBC.com

For patients who do not achieve pCR, visit NoPCRinEBC.com

*There may be other treatment options available for your patients.

More Innovation Is on Tap for 2021
Five Experts Describe Key Trends

by ONCLIVE® STAFF

Five experts in oncology research detail their expectations for emerging therapeutic strategies likely to influence clinical practice this year, particularly in breast, lung, genitourinary, and hematologic malignancies. Weighing in on these developments are Howard A. “Skip” Burris III, MD; Debu Tripathy, MD; Balazs Halmos, MD, MS; Neeraj Agarwal, MD; and Lori A. Leslie, MD.

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By Maurie Markman, MD

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DURING THE PAST 30 YEARS, we’ve grown accustomed to waves of innovation in oncology that have enhanced outcomes for patients in ways that once seemed unimaginable. As 2021 gets rolling, we can celebrate advancements in cancer care that occurred during a year in which we faced the most challenging public health crisis of our lifetimes and look forward to more promising developments in the months ahead.

As in all areas of medicine dealing with the sweeping impact of the coronavirus disease 2019 (COVID-19) pandemic, the oncology field had to adjust how it delivered care, conducted clinical research, and shared information with patients and colleagues.

Although there are many facets of this impact, we’d like to focus here on research. COVID-19 shut down many research projects, at least temporarily. For example, the American Cancer Society reported in May 2020 that more than half of its grantees had their projects halted.1 Against such a backdrop, the research achievements of the past year and the outlook for 2021 are particularly noteworthy.

In this issue of OncologyLive®, we feature oncology leaders sharing their insights about the past year’s highlights and ongoing clinical research that is likely to yield results in 2021. The good news is that we can expect continued expansion of molecularly targeted therapies and immunotherapies, 2 modalities that have evolved tremendously since the 1990s.

One particularly exciting area involves antibody-drug conjugates (ADCs). In 2009, there was only 1 FDA-approved ADC in clinical practice, gemtuzumab ozogamicin (Mylotarg), which was voluntarily withdrawn from the market in 2010 before being reintroduced in 2017. Now, there are 9 ADCs available for clinical use in oncology and more than 80 others under study.2 Further developments involving recently approved ADCs such as fam-trastuzumab deruxtecan-nxki (Enhertu) and sacituzumab govitecan-hziy (Trodelvy) are on the horizon.

It is critical to remember that there is an infrastructure supporting these research efforts and that investigators have been soldiering on despite COVID-19. As 2021 opens, public health experts are warning that more dark days lie ahead in the pandemic even as they celebrate the introduction of vaccines that will help us regain our footing.

We’d like to start the year on a positive note by recognizing the innovation that we’ve been fortunate to witness even amid the pandemic. The editorial team at OncLive® has introduced many new features to keep the information flowing throughout this challenging time, available 24/7 at OncLive.com.

We look forward to another productive year.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
18th Annual Winter Lung Cancer Conference
VIRTUAL, INTERACTIVE CONFERENCE
FEBRUARY 5-7, 2021

Virtual, Interactive Conference
FEBRUARY 5-7, 2021

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HOT TOPICS

• Integration and optimization of molecular testing throughout the continuum of disease
• Leveraging the growing therapeutic armamentarium for oncogene-driven non–small cell lung cancer (NSCLC)
• Navigating options for first-line immunotherapy-based regimens in metastatic NSCLC
• Application of consolidation immunotherapy in locally advanced NSCLC
• Current approaches with surgery and radiation oncology in patients with thoracic malignancies

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• Submit and discuss questions and challenging cases in real time

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Acknowledgment of Commercial Support
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DURING THE PAST DECADE, we have witnessed substantial achievements in the treatment of patients with advanced malignant disease. Although these benefits do not pertain to all cancers and “cure” remains a relatively uncommon event, oncologists have an increasing number of molecularly targeted and immunotherapeutic strategies to employ based on objectively meaningful clinical trial outcomes.

Unfortunately, despite the acceleration in regulatory approval of effective strategies, we continue to see reports in the peer-reviewed literature lamenting the lack of robust overall survival (OS) benefits documented in phase 3 randomized trials. For example, a recent report examined FDA approval of anticancer therapeutics between 2000 and 2016 and concluded that despite the fact that these agents caused “substantial tumor responses,” they were “associated with...prolonging median overall survival by only 2.4 months.”

Even in settings in which progression-free survival (PFS) has been accepted as a valid end point for regulatory approval, such as antineoplastic therapy for advanced ovarian cancer, some continue to inquire whether this outcome can serve as a reliable surrogate for OS. This discussion fails to acknowledge the increasing relevance of the chronic disease nature of many cancers and the potentially substantial impact of multiple therapeutic options once an individual patient ceases treatment on a given clinical trial.

Several examples emphasize this critical point. Findings from 2 second-line ovarian cancer chemotherapy trials conducted for regulatory purposes and initiated 8 years apart (1999 and 2007) had the same eligibility (and ineligibility) criteria and included an identical carboplatin/gemcitabine chemotherapy treatment arm. Although cross-trial comparisons must always be conducted with caution, it is notable that these studies were carefully monitored (as required by regulatory agencies) and resulted in essentially the same median PFS outcomes (median 8.6 and 8.4 months, respectively). Although similar outcomes would have been anticipated for similar or identical treatment regimens, OS findings observed for these 2 study populations were strikingly different. For the carboplatin/gemcitabine trial regimen initiated in 1999, the median OS was 18.0 months, whereas it was almost twice as long—35.2 months—for the same regimen employed in a study started 8 years later.

Although a definitive reason for why survival was so much longer in the later study is not possible to discern, the most likely is the availability of an increasing number of potentially beneficial therapeutic agents employed either on or off label following removal of research participants from the phase 3 trial.
A second excellent example of the increasing utility of later lines of therapy and their impact on an OS end point in a phase 3 randomized trial is provided by data involving therapy for metastatic melanoma. In an analysis of 9 randomized trials that employed a dacarbazine control arm with no crossover to the experimental regimen, there was a very strong correlation between PFS and OS (correlation coefficient, 0.96). However, when trials were included that permitted crossover from dacarbazine to the effective experimental regimen, the correlation coefficient between PFS and OS decreased to 0.55.5

And in a more recent report of 5-year outcomes observed in patients with wild-type BRAF advanced melanoma treated with nivolumab (Opdivo) versus a control arm of dacarbazine, investigators found strikingly improved 5-year PFS for patients treated with the checkpoint inhibitor (28% vs 3%). This translated into improved 5-year OS for the nivolumab-treated population (39% vs 17%). The overall response rate was, not surprisingly, also superior in the nivolumab study arm (42% vs 14%).6

However, the 5-year OS rate of patients initially treated with dacarbazine in this study but who subsequently received additional therapy, including nivolumab, was 38%, essentially no different from that of the group who received the checkpoint inhibitor as primary treatment. This outcome occurred despite the substantially inferior PFS observed with dacarbazine during the trial.

Of course, the appropriate conclusion here is not that nivolumab failed to improve OS despite its influence on time to disease progression, but rather that despite the objectively poor primary trial outcome (PFS) associated with the almost inactive chemotherapeutic (dacarbazine), effective therapy delivered after completion of the study regimen was able to have an impressively favorable influence on individual participants’ ultimate survival. ■

REFERENCES
IF SHE RESPONDS TO CHEMOTHERAPY

ZEJULA is the only once-daily, oral, first-line maintenance monotherapy approved for advanced ovarian cancer in complete or partial response to platinum-based chemotherapy, regardless of biomarker status\(^1^3\)

**Indication**

ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

**Important Safety Information**

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 33%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA.

Closely monitor patients with cardiovascular disorders, decreased appetite (19%), dizziness (19%), fatigue (25%), insomnia (25%), vomiting (22%), dyspnea (22%), nausea (22%), and pain (39%). Leukopenia (28%), headache (26%), and decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased cholesterol (29%), increased AST (35%), and increased ALT (29%) have been reported. In PRIMA, the overall incidence of Grade ≥3 elevation of AST/ALT were reported, respectively, in 46%, 23%, and 12% of patients. Do not start ZEJULA until patients have recovered from laboratory abnormalities caused by prior chemotherapy (≤Grade 1). Monitor common lab abnormalities periodically thereafter during treatment with ZEJULA. If toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.
PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS¹,⁴

**OVERALL POPULATION**

<table>
<thead>
<tr>
<th><strong>REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH</strong></th>
</tr>
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<tr>
<td><strong>38%</strong></td>
</tr>
</tbody>
</table>

MEDIAN PFS: 13.8 MONTHS WITH ZEJULA VS 8.2 MONTHS WITH PLACEBO (HR 0.62; 95% CI 0.50-0.76) P <0.0001

**Study Design:** PRIMA, a randomized double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of once-daily ZEJULA versus placebo (2:1) in 733 women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following a CR or PR to first-line platinum-based chemotherapy. The primary endpoint was a hierarchical calculation of PFS: first in patients with HRd tumors and then in all patients. PFS was measured from time of randomization to time of disease progression or death. At the time of PFS analysis, limited overall survival data were available with 11% deaths in the overall population.¹⁴

**Important Safety Information (continued)**

especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

**Embryo-Fetal Toxicity and Lactation:** Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

**The most common adverse reactions** (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia, (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

**Common lab abnormalities** (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

**References:**

1L, first-line; CI, confidence interval; CR, complete response; HR, hazard ratio; HRd, homologous recombination deficient; PFS, progression-free survival; PR, partial response.

Visit ZEJULA.COM/HCP to explore the PRIMA data.

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NRP/RNA2000007 August 2020
Produced in USA.

Please see Brief Summary on the following pages.
Do not start ZEJULA until patients have recovered from hematologic toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematologic toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics (see Dosage and Administration (2.3) of full prescribing information).

5.3 Cardiovascular Effects

Hypertension and hypertensive crisis have been reported in patients treated with ZEJULA.

In PRIMA, Grade 1-4 hypertension occurred in 6% of ZEJULA-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 531 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypotension.

In NOVA, Grade 1-4 hypertension occurred in 5% of ZEJULA-treated patients compared to 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypotension occurred in <1% of patients.

In QUADRA, Grade 1-4 hypertension occurred in 5% of ZEJULA-treated patients with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypotension occurred in <2% of patients.

Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Clinically monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypotension. Medically manage hypertension and antihypertensive medications and adjustment of the ZEJULA dose, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA (see Use in Specific Populations (8.1, 8.3)).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (see Warnings and Precautions (5.12))
- Bone Marrow Suppression (see Warnings and Precautions (5.2))
- Cardiac Effects (see Warnings and Precautions (5.3))

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 most common adverse reactions of all grades in >10% of patients who received ZEJULA in the placebo-controlled trials included:

- Anemia (16.5%)
- Fatigue (14.7%)
- Nausea (9.7%)
- Vomiting (8.7%)

In placebo-controlled studies, the following adverse reactions occurred in >2% of patients receiving ZEJULA and >1% of patients receiving placebo and were more common in patients receiving ZEJULA:

- Anemia
- Fatigue
- Nausea
- Vomiting

In NOVA, the median duration of treatment was 11.1 months (range: 0.6 to 26 months).

Table 1. Adverse Drug Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ZEJULA N=844</th>
<th>Placebo N=364</th>
<th>ZEJULA N=844</th>
<th>Placebo N=364</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66 (41.3%)</td>
<td>5 (1.4%)</td>
<td>65 (76.1%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (18.9%)</td>
<td>9 (2.5%)</td>
<td>16 (19.5%)</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52 (62.2%)</td>
<td>21 (5.8%)</td>
<td>52 (62.2%)</td>
<td>21 (5.8%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>58 (68.6%)</td>
<td>9 (2.5%)</td>
<td>58 (68.6%)</td>
<td>9 (2.5%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nausea</td>
<td>57 (67.8%)</td>
<td>2 (0.5%)</td>
<td>57 (67.8%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>40 (47.2%)</td>
<td>1 (0.3%)</td>
<td>40 (47.2%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (26.2%)</td>
<td>1 (0.3%)</td>
<td>22 (26.2%)</td>
<td>1 (0.3%)</td>
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<tr>
<td>General Disorders and</td>
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<tr>
<td>Administration Site Conditions</td>
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</tr>
<tr>
<td>Fatigue</td>
<td>51 (60.3%)</td>
<td>4 (1.1%)</td>
<td>51 (60.3%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
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<tr>
<td>AST/ALT elevation</td>
<td>14 (16.7%)</td>
<td>3 (0.8%)</td>
<td>14 (16.7%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Metabolism and Nutritional</td>
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<tr>
<td>Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>19 (22.6%)</td>
<td>1 (0.3%)</td>
<td>19 (22.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective</td>
<td></td>
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<tr>
<td>Tissue Disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Muscle-skeletal pain</td>
<td>39 (46.3%)</td>
<td>1 (0.3%)</td>
<td>39 (46.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
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</tr>
<tr>
<td>Headache</td>
<td>26 (31.2%)</td>
<td>4 (1.1%)</td>
<td>26 (31.2%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>19 (22.6%)</td>
<td>0 (0.0%)</td>
<td>19 (22.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>25 (30.0%)</td>
<td>1 (0.3%)</td>
<td>25 (30.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>32 (38.5%)</td>
<td>5 (1.4%)</td>
<td>32 (38.5%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mediastinal Disorders</td>
<td></td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>22 (26.2%)</td>
<td>1 (0.3%)</td>
<td>22 (26.2%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (21.7%)</td>
<td>0 (0.0%)</td>
<td>18 (21.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (21.7%)</td>
<td>7 (1.9%)</td>
<td>18 (21.7%)</td>
<td>7 (1.9%)</td>
</tr>
</tbody>
</table>

All adverse reactions in the table consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache and insomnia, which are single preferred terms.

*ICD-10=International Classification of Diseases, 10th Revision

Includes uses, indications, contraindications, warnings, precautions, adverse reactions, and drug interactions of ZEJULA.
Table 2: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELURA in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic Abnormalities</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>87</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40</td>
</tr>
<tr>
<td>Maintenance of Renal Function</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions Reported in ≥10% of Patients Receiving ZELURA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54</td>
</tr>
<tr>
<td>Anemia</td>
<td>50</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>36</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>53</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>44</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 4: Abnormal Laboratory Findings in ≥25% of All Patients Receiving ZELURA in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 5: Adverse Reactions Reported in ≥10% of Patients Receiving ZELURA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>74</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 6: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELURA in NOVA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA</td>
<td>Placebo</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>85</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>72</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
<td>66</td>
</tr>
<tr>
<td>Increase in AST</td>
<td>59</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>28</td>
</tr>
</tbody>
</table>

- Number of patients, WBC = white blood cells; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase.
- The following adverse reactions are laboratory abnormalities that have been identified in ≥10% of the 167 patients receiving ZELURA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, alkalosis, neutropenia, elevated blood ALT.
alkaline phosphatase increased, weight decreased, depression, epistaxis.

**Treatment of Advanced Ovarian Cancer After Three or More Chemotherapies**

The safety of ZELJUA monotherapy 300 mg once daily has been studied in QUADRA, a single-arm study in 468 patients with recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more prior lines of therapy. The median duration of overall study treatment was 3 months (range: 0.03 to 12 months). For the indicated QUADRA population, the median duration was 4 months (range: 6.1 to 30 months).

Fetal adverse reactions occurred in 2% of patients, including cardiac arrest.

Serious adverse reactions occurred in 43% of patients receiving ZELJUA. Serious adverse reactions in >1% of patients were small intestinal obstruction (7%), vomiting (6%), nausea (5%), and abdominal pain (4%).

Permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 21% of patients who received ZELJUA.

Adverse reactions led to dose reduction or interruption in 33% of patients receiving ZELJUA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZELJUA were thrombocytopenia (43%), anemia (21%), neutropenia (11%), nausea (13%), vomiting (11%), fatigue (9%), and abdominal pain (5%).

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZELJUA in QUADRA.

**Table 7. Adverse Reactions Reported in ≥10% of Patients Receiving ZELJUA in QUADRA**

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>51%</td>
<td>27%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52%</td>
<td>28%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>67%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44%</td>
<td>8%</td>
</tr>
<tr>
<td>Constipation</td>
<td>36%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

**General Disorders and Administration Site Conditions**

| Fatigue                             | 56%       | 7%         |
| Infecions and Infestations          | 15%       | 2%         |
| Urinary tract infection             | 15%       | 2%         |
| Blood alkaline phosphatase increased| 11%       | 2%         |
| AST/ALT elevation                   | 11%       | 1%         |
| Metabolism and Nutrition Disorders  |           |            |
| Decreased appetite                  | 27%       | 2%         |
| Musculoskeletal and Connective Tissue Disorders | | |
| Musculoskeletal pain                | 29%       | 3%         |
| Nervous System Disorders            |           |            |
| Headache                            | 19%       | 0.4%       |
| Dizziness                           | 11%       | 0%         |
| Psychiatric Disorders               | 23%       | 1%         |
| Renal and Urinary Disorders         |           |            |
| Acute kidney injury                 | 17%       | 1%         |
| Respiratory, Thoracic and Mediastinal Disorders | |
| Dyspnea                             | 22%       | 3%         |
| Cough                               | 13%       | 0%         |
| Vascular Disorders                  |           |            |
| Hypertension                        | 14%       | 5%         |

*CDCAE*—Common Terminology Criteria for Adverse Events version 4.02.

Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutrophil infection and neutrophil sepsis.

<table>
<thead>
<tr>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=663</td>
<td>N=663</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>83%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53%</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46%</td>
</tr>
<tr>
<td>Decreased alkaline phosphatase</td>
<td>40%</td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36%</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34%</td>
</tr>
<tr>
<td>Increased neutrophils</td>
<td>34%</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>29%</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27%</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZELJUA. 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.

Immune System Disorders: hypersensitivity (including anaphylaxis), lymphadenopathy, neutropenia, thrombocytopenia, anemia, neutropenia, and abdominal pain.

Table 7 and Table 8 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with ZELJUA in QUADRA.

6.8 Pregnancy

**Risk Summary**

Based on its mechanism of action, ZELJUA can cause fetal harm when administered to pregnant women [see Clinical Pharmacology (12.1) of full prescribing information]. There are no data regarding the use of ZELJUA in pregnant women to inform the drug-associated risks. ZELJUA has the potential to cause teratogenicity and embryofetal death since nirasiparib is genotoxic and targets actively dividing cells in animals and patients. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
FDA DIGEST

First COVID-19 Vaccines Are Cleared for Emergency Use

Two vaccines were granted emergency use authorization by the FDA to prevent coronavirus disease 2019 (COVID-19). The first authorization, given to Pfizer Inc and BioNTech SE for BNT162b2 was specified for individuals aged 16 years and older. Findings from a pivotal phase 3 trial (NCT04368728) showed that among 43,448 patients, the vaccine had 95% efficacy (95% CI, 90.3%-97.6%) in preventing COVID-19 infection in individuals without prior infection 7 days or more after the second vaccine dose.

The second authorization was given to the Moderna COVID-19 vaccine for individuals aged 18 years and older. Data from a phase 3 trial of 27,817 individuals showed a vaccine efficacy of 94.5% (95% CI, 86.5%-97.8%) in preventing confirmed COVID-19 infection occurring at least 2 weeks following the second vaccine dose.

Because the initial US supply of the COVID-19 vaccine is expected to be limited, the Centers for Disease Control and Prevention recommends that health care personnel and long term-care facility residents receive the first doses, based on recommendations from the Advisory Committee on Immunization Practices, an independent panel of medical and public health experts. As vaccine availability increases, recommendations will expand to include more groups.

PET-Imaging Agent Gallium 68 PSMA-11 Gains Approval for Prostate Cancer

The FDA has approved Gallium 68 PSMA-11 (Ga 68 PSMA-11), the first drug for PET imaging of prostate-specific membrane antigen–positive lesions in patients with prostate cancer. The indication specifies the use of the radioactive diagnostic for patients with suspected prostate cancer metastasis who are potentially curable via surgery or radiation therapy and for those with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen levels.

Ga 68 PSMA-11 was investigated in 2 clinical trials that collectively enrolled 960 patients with prostate cancer; these patients were each given 1 injection of the PET imaging agent. Among the 325 patients in the first trial who proceeded to surgery, those with positive readings in the pelvic lymph nodes on Ga 68 PSMA-11 PET had a positive predictive value of 61% (95% CI, 41%-81%). In the second trial, of 635 patients with rising serum prostate-specific antigen levels after initial prostate surgery or radiotherapy, 74% had at least 1 positive lesion detected by Ga 68 PSMA-11 PET in at least 1 body region.

The identification of positive lesions prior to treatment may spare certain patients from undergoing unnecessary surgery.

Belumosudil Undergoes Priority Review for Chronic GVHD

The FDA has granted a priority review designation to a new drug application for belumosudil (KD025) for the treatment of patients with chronic graft-vs-host disease (GVHD). Belumosudil is a selective oral inhibitor of ROCK2, a signaling pathway that modulates inflammatory response and profibrotic processes.

Findings from the ROCKstar Study (NCT03640481), which evaluated belumosudil in patients with chronic GVHD who had received 2 or more prior lines of therapy, will provide the evidence for the approval. Results showed that in patients who received the agent at a 200-mg once-daily dose and 200-mg twice-daily dose, the objective response rates were 73% (95% CI, 60%-83%; P < .0001) and 74% (95% CI, 62%-84%; P < .0001), respectively. Further, as of data cutoff in May 2020, the median duration of response had not yet been reached, with 49% of responding patients maintaining their response for at least 20 weeks. The FDA is expected to make a decision by May 30.

Sotorasib Review Moves Forward for KRAS G12C–Mutant NSCLC

A new drug application has been submitted to the FDA for sotorasib (formerly AMG 510) for use as a potential treatment in patients with KRAS G12C–mutated locally advanced or metastatic non–small cell lung cancer (NSCLC), as determined by an FDA-approved test, after at least 1 previous systemic therapy.

Prior to the submission the FDA granted breakthrough therapy designation to the agent supported by data from the phase 2 CodeBreak 100 trial (NCT03600883). Findings showed that sotorasib elicited durable responses in 56 patients with KRAS G12C–mutant advanced NSCLC who had progressed on a median of 2 prior lines of treatment. More than 50% of patients who responded to sotorasib continued to respond and were still on treatment at data cutoff, according to Amgen, the agent’s developer.

The primary endpoint for the phase 2 study was centrally assessed objective response rate. Further, the company reports that the safety and tolerability findings of the phase 2 trial were similar to previously reported phase 1 data. Those data, presented at the European Society for Medical Oncology Congress 2020, showed that among 59 patients with NSCLC, the small-molecule inhibitor elicited a confirmed overall response rate of 32.2%, with a disease control rate of 88.1% and tumor reduction observed across all dose levels.

Detailed data from the phase 2 trial is expected to be presented at the 2021 International Association for the Study of Lung Cancer World Conference.

Zanidatamab Gains Ground in HER2+ Biliary Tract Cancer

The FDA has granted a breakthrough therapy designation to zanidatamab for the treatment of patients with HER2 gene–amplified biliary tract cancer who have received prior therapy.

The designation is based on an ongoing phase 1 study (NCT02892123) of zanidatamab in patients with locally advanced, unresectable and/or metastatic HER2-expressing cancers, including biliary tract cancer. Findings from the trial will be presented at the 2021 Gastrointestinal Cancers Symposium in January.

Zanidatamab is a bispecific antibody designed with biparatopic binding, which results in dual HER2 signal blockade, increased binding, removal of HER2 protein from the cell surface, and potent effector function, which can lead to activity in patients. Prior to the breakthrough therapy designation, the FDA granted 2 fast track designations to zanidatamab: as a single agent for refractory biliary tract cancer and in combination with standard-of-care chemotherapy for first-line gastroesophageal adenocarcinoma.
**Drug Spotlight | BELANTAMAB MAFODOTIN-BLMF (BLENREP)**

**First BCMA-Targeting Therapy Debuts in Multiple Myeloma**

by ANITA T. SHAFFER

**THE APPROVAL OF BELANTAMAB MAFODOTIN-BLMF**

(Blenrep) for patients with refractory multiple myeloma marks the first therapy directed at B-cell maturation antigen (BCMA), a target of robust research interest, to reach clinical practice. The FDA granted an accelerated approval for the agent on August 5, 2020, for adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent."¹

The decision was based on findings from the ongoing phase 2 DREAMM-2 study (NCT03525678), which tested 2 dosing levels of belantamab mafodotin in patients who were heavily pretreated. The approval stemmed from an overall response rate (ORR) of 31% (97.5% CI, 21%-43%) among 97 patients who received the recommended dose of 2.5 mg/kg administered intravenously once every 3 weeks. Responses persisted for 6 months or longer in 73% of responders.¹

After 13 months of follow-up, responses rates were similar regardless of the number of prior lines of therapy that participants had received, according to findings from a post hoc analysis presented at the virtual 62nd American Society of Hematology Annual Meeting and Exposition in December 2020 (ASH 2020). For those who had received 3 to 6 lines of prior therapy, the ORR was 34% with a median duration of response of 11.0 months (95% CI, 4.2-Not reached [NR]), and the median overall survival was 13.7 months (95% CI, 9.1-NR). For patients who had 7 or more previous treatments, the ORR was 30% with a median response duration of 13.1 months (95% CI, 4.0-NR), and median overall survival of 13.4 months (95% CI, 8.7-NR).²

Belantamab mafodotin, which is an antibody-drug conjugate, "represents a useful treatment option for relapsed/refractory multiple myeloma, including patients with a high burden of prior treatment for whom prognosis is otherwise poor," Sagar Lonial, MD, the lead investigator in the DREAMM-2 study, said in presenting the updated data at ASH 2020. Such patients, Lonial said, typically experience a decrease in the depth of response and shorter remissions as they progress in their disease.²

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Lonial, a 2020 Giants of Cancer Care® award winner, is chief medical officer at Winship Cancer Institute of Emory University in Atlanta, Georgia. He also is professor and chair of the Department of Hematology and Medical Oncology and the Anne and Bernard Gray Family Chair in Cancer, both at Emory University School of Medicine. In an interview with OncologyLive®, Lonial discussed key facets of belantamab mafodotin and potential next steps.

Some investigators have said that successful targeting of BCMA would be a transformative development for multiple myeloma therapy. Would you agree?

Yes. I think the advantage that BCMA has over, for instance, CD38, or even SLAMF7 is that the target is expressed much more exclusively on plasma cells, so the off-target impact is going to be less. Signaling through BCMA is 1 of the reasons multiple myeloma cells proliferate and are drug resistant. Blocking BCMA not only targets the tumor cell, but it also may help to overcome drug resistance.

Please describe the patient population for this drug.

The FDA approval is for patients who are triple-class refractory, so [the patient ideally would be] resistant to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 antibodies. For me, it would be a patient who has had 3 prior lines of therapy and still has a reasonable performance status to get any treatment at all. My go-to in that situation, if not a clinical trial, would be belantamab mafodotin.

Belantamab mafodotin was approved with a boxed warning about the risk of ocular toxicity. Could you discuss this adverse event?

The ocular toxicity is somewhat unique for myeloma drugs. It is more of an exam finding by an ophthalmologist or an optometrist; it does not always result in significant symptoms. In fact, only in 18% to 20% of the time [does it actually result] in change in visual acuity.

I think the take-home messages are that [the agent] is a really good option for triple-class refractory myeloma and, importantly, partnering with an eye care professional is part of the process. It’s something we should get used to doing in order to figure out how to maximize the benefit from belantamab.

The best way to treat [an ocular effect] is to hold the drug and let the patient recover from the toxicity. What I think is important and different from many other drugs, though, is that the half-life of belantamab mafodotin is long enough that even if you have to hold a dose or 2 for 3 weeks, or oftentimes 6 weeks, most patients still maintain or improve their response. So, it’s not as though if you don’t stay on schedule you’re going to be in trouble.

Are there immunogenic qualities to belantamab mafodotin?

Yes, it does induce immunogenic cell death. As such, it’s being tested right now in partnership with for instance, pembrolizumab [Keytruda; DREAMM-4; (NCT03848845)] to see whether that immunogenic cell death in combination with a checkpoint inhibitor may activate an innate T-cell response separate from the effect directly of the development.

What are some unanswered questions about this drug?

I think the question is going to be, how do you partner [BCMA-targeting agents] with other drugs? Those trials are being done now, combining it with pomalidomide [Pomalyst], with bortezomib [Velcade], with lenalidomide [Revlimid]. How you sequence [the drugs] is another question that’s coming up. If you’ve had 1 [anti-BCMA drug], can you respond to another?

That’s a question we’ve not been able to answer because most of the trials have excluded prior exposure to BCMA. But now they’re including cohorts of prior BCMA therapy. So I think we’ll get an answer to that question in the next year.²

**REFERENCES**


FDA grants accelerated approval to belantamab mafodotin-blmf (Blenrep) for the treatment of adults with relapsed or refractory multiple myeloma (R/R MM) who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Mechanism of action:
- Belantamab mafodotin is an antibody-drug conjugate comprised of a B-cell maturation antigen (BCMA)-directed monoclonal antibody connected via a protease-resistant linker to the microtubule inhibitor monomethyl auristatin F.

Dosing:
- 2.5 mg/kg as an intravenous infusion over approximately 30 minutes once every 3 weeks
- Each 100-mg vial is reconstituted with 2 mL of sterile water for injection to obtain a final concentration of 50 mg/mL.
- An ophthalmic exam should be performed prior to initiation of therapy and during treatment.

How supplied:
- Lyophilized powder in a 100-mg, single-dose vial for reconstitution and further dilution

Company: GlaxoSmithKline

**PIVOTAL CLINICAL TRIAL**

The DREAMM-2 (NCT03525678) trial enrolled patients with R/R MM previously treated with 3 or more prior therapies, including an anti-CD38 monoclonal antibody, and who were refractory to an immunomodulatory agent and a proteasome inhibitor. FDA approval was based on a cohort of 97 patients who received belantamab mafodotin at 2.5 mg/kg administered intravenously every once 3 weeks.

**BASELINE PATIENT CHARACTERISTICS**

**EFFICACY POPULATION (N = 97)**

<table>
<thead>
<tr>
<th>Median age (range)</th>
<th>65 (39-85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy completed at screening</td>
<td></td>
</tr>
<tr>
<td>3 lines</td>
<td>5%</td>
</tr>
<tr>
<td>4 lines</td>
<td>11%</td>
</tr>
<tr>
<td>5 lines</td>
<td>18%</td>
</tr>
<tr>
<td>6 lines</td>
<td>14%</td>
</tr>
<tr>
<td>7 lines</td>
<td>20%</td>
</tr>
<tr>
<td>8 lines</td>
<td>14%</td>
</tr>
<tr>
<td>9 lines</td>
<td>6%</td>
</tr>
<tr>
<td>10 lines</td>
<td>5%</td>
</tr>
<tr>
<td>&gt; 10 lines</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Stage at screening**

- I - 22%
- II - 34%
- III - 43%
- Unknown - 1%

**Disease characteristics**

- 23% Yes
- 29% No
- 77% No
- 71% Yes

**EXTRAMEDULLARY DISEASE**

- 77% No

**LYTIC BONE LESIONS**

- 71% Yes

**REFERENCES**


**EFFICACY RESULTS IN THE DREAMM-2 TRIAL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Belantamab mafodotin (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (97.5% CI)</td>
<td>31% (21%-43%)</td>
</tr>
<tr>
<td>Stringent complete response rate</td>
<td>2%</td>
</tr>
<tr>
<td>Complete response</td>
<td>1%</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>15%</td>
</tr>
<tr>
<td>Partial response</td>
<td>12%</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>NR (NR-NR)</td>
</tr>
</tbody>
</table>

**DOR**, duration of response; NR, not reached.

**BOXED WARNING**

- **Ocular toxicity:** changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes have occurred. Ophthalmic exams should be conducted at baseline and prior to each dose. Treatment should be withheld until improvement or permanently discontinued, based on severity.

**OTHER WARNINGS AND PRECAUTIONS**

- Thrombocytopenia
- Infusion-related reactions
- Embryo-fetal toxicity

**COMMONLY REPORTED ADVERSE EFFECTS IN DREAMM-2 TRIAL**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Belantamab mafodotin (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Keratopathy</td>
<td>71%</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>62%</td>
</tr>
<tr>
<td>Decreased visual activity</td>
<td>53%</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>32%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>22%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22%</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>21%</td>
</tr>
</tbody>
</table>
TAZVERIK is indicated for the treatment of:

• Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

• Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

• **Secondary Malignancies**
  The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

• **Embryo–Fetal Toxicity**
  Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0–45h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

**Adverse Reactions**

In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily: Serious adverse reactions occurred in 30% of patients who
TAZVERIK® (tazemetostat)

THE OBJECTIVES OF THIS PROGRAM ARE TO:

- Raise awareness of TAZVERIK's indication for patients with relapsed or refractory follicular lymphoma
- Review the mechanism of action of TAZVERIK
- Discuss TAZVERIK's clinical trial data, including its efficacy and safety profile
- Provide information pertaining to dosing of TAZVERIK, drug interactions, use in special patient populations, and patient counseling information
- Review a hypothetical patient case

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Rocky Mountain Cancer Centers

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The University of Arizona and Arizona Cancer Center

received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions
Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose.
Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK, which may decrease the efficacy of TAZVERIK.
Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation
Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Please see the Brief Summary of the Prescribing Information on the next pages.
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION
Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE - TAZVERIK is indicated for the treatment of patients with relapsed or refractory (RR) follicular lymphoma (FL) who have received at least 2 prior systemic therapies. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSEAGE AND ADMINISTRATION
Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicities. Swallow tablets whole. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose. Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>600 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>400 mg orally twice daily</td>
</tr>
</tbody>
</table>

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia [see Adverse Reactions]</td>
<td>Neutrophil count less than 1 x 10^9/L</td>
<td>Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline. For first occurrence, resume at same dose. For second and third occurrence, resume at reduced dose. Permanently discontinue after fourth occurrence.</td>
</tr>
<tr>
<td>Thrombocytopenia [see Adverse Reactions]</td>
<td>Platelet count less than 50 x 10^9/L</td>
<td>Withhold until platelet count is greater than or equal to 75 x 10^9/L or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td>Anemia [see Adverse Reactions]</td>
<td>Hemoglobin less than 8 g/dL</td>
<td>Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.</td>
</tr>
<tr>
<td>Other adverse reactions [see Adverse Reactions]</td>
<td>Grade 3</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first and second occurrence, resume at reduced dose. Permanently discontinue after third occurrence.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Withhold until improvement to at least Grade 1 or baseline. For first occurrence, resume at reduced dose. Permanently discontinue after second occurrence.</td>
</tr>
</tbody>
</table>

Dosage Modifications for Drug Interactions
Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

<table>
<thead>
<tr>
<th>Current Dosage</th>
<th>Adjusted Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg orally twice daily</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>600 mg orally twice daily</td>
<td>400 mg for first dose and 200 mg for second dose</td>
</tr>
<tr>
<td>400 mg orally twice daily</td>
<td>200 mg orally twice daily</td>
</tr>
</tbody>
</table>

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>3.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>2.0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0.0</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>15</td>
<td>5.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>5.0</td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections and infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15</td>
<td>0.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 6 continues on the next page.

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS
Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 688 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.6% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL).

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC_{0-24}]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions], Clinical Trial 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 practice. The safety of TAZVERIK was evaluated in patients with relapsed or refractory follicular lymphoma enrolled in Cohorts 4 and 5 of Study E7438-G000-101 [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients receiving TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for greater than one year, and 21% were exposed for 18 months or longer. Serious adverse reactions occurred in 30% of patients receiving TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, sepsis, and anemia. Eight patients (8%) permanently discontinued TAZVERIK due to an adverse reaction. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. The most frequent adverse reactions requiring dosage interruptions in ≥3% of patients were thrombocytopenia and anaemia. Dose reduction due to an adverse reaction occurred in 9 patients (9%) who received TAZVERIK. The most frequent adverse reaction requiring dose reduction in ≥3% of patients was anemia. The most common adverse reaction (≥20%) was nausea. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in Cohorts 4 and 5 of Study E7438-G000-101.

Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>2.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>19</td>
<td>3.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>2.0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0.0</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>15</td>
<td>5.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>5.0</td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections and infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15</td>
<td>0.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Table 6 continues on the next page.
Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors
[see Drug Interactions, Clinical Pharmacology]
the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of

Table 7. Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Relapsed/Refractory Follicular Lymphoma Receiving TAZVERIK in Study E7438-G000-101

![Table](https://via.placeholder.com/150)

**Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Receiving Tazemetostat in Cohorts 4 and 5 of Study E7438-G000-101 (continued)**

### Laboratory Abnormality

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAZVERIK*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td></td>
<td>Hematology</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Chemistry</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.

**DRUG INTERACTIONS**

Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A Inhibitors: Coadministration of TAZVERIK with a strong or moderate CYP3A inhibitor increases tazemetostat plasma concentrations [see Clinical Pharmacology], which may increase the frequency or severity of adverse reactions. Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK. If coadministration of moderate CYP3A inhibitors cannot be avoided, reduce TAZVERIK dose [see Dosage and Administration]. Strong and Moderate CYP3A Inducers: Coadministration of TAZVERIK with a strong or moderate CYP3A inducer may decrease tazemetostat plasma concentrations [see Clinical Pharmacology], which may decrease the efficacy of TAZVERIK. Avoid coadministration of moderate and strong CYP3A inducers with TAZVERIK.

Effect of TAZVERIK on Other Drugs - CYP3A Substrates: Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see Use in Specific Populations, Clinical Pharmacology].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy** - Risk Summary: Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC[app]] at the 800 mg twice daily dose (see Data). Advise pregnant 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: In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses of ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, domed heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after once daily oral administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

Lactation - Risk Summary: There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Females and Males of Reproductive Potential - Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see Use in Specific Populations]. Risk Summary: TAZVERIK can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Contraception: Females - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see Drug Interactions]. Males - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

**Pediatric Use** - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.

**Juveme Animal Toxicity Data** - In a 13-week juvenile rat toxicity study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)
- Distorted testicles in males at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

**Geriatric Use** - Of the 90 patients with relapsed or refractory follicular lymphoma who received TAZVERIK in Study E7438-G000-101, 44% were ≥65 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients.

**Renal Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end stage renal disease [see Clinical Pharmacology].

**Hepatic Impairment** - No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN). TAZVERIK has not been studied in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment [see Clinical Pharmacology].

**NONCLINICAL TOXICOLOGY**

Carcinogenesis, Mutagenesis, Impairment of Fertility - Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration dosing. Tazemetostat did not cause genetic damage in a standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vitro micronucleus assessment in human peripheral blood lymphocytes, and an in vivo micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Tazemetostat did not result in any notable effects in the adult male and female reproductive organs [see Use in Specific Populations].

**PATIENT COUNSELING INFORMATION** - Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Secondary Malignancies: Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see Warnings and Precautions].

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations]. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations, Nonclinical Toxicology].

Lactation: Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see Use in Special Populations].

**Drug Interactions** - Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK [see Drug Interactions].

Brief Summary 07/2020
TZA-BR-000097
Rx Only
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The development of additional molecularly targeted therapies and the search for enhanced immunotherapy regimens are expected to permeate the oncology landscape across a broad range of malignancies as 2021 unfolds, according to experts. Those were among the key trends for the New Year that experts in breast, lung, genitourinary, and hematologic malignancies described in interviews with OncologyLive®. Many of the expectations for the coming year grew out of the advances of 2020, in which new targeted therapies emerged for patient subsets across multiple tumor types and novel immunotherapies continued to expand.

These developments include FDA approvals for the first RET inhibitors, selpercatinib (Retevmo) and pralsetinib (Gavreto), in non-small cell lung cancer (NSCLC) and thyroid cancer settings, and a third chimeric antigen receptor (CAR) T-cell therapy for an oncology indication, brexucabtagene autoleucel (Tecartus), for mantle cell lymphoma.

Continuing progress in the optimal use of antibodies aimed at immune checkpoints is also anticipated. This year will mark a decade since the first checkpoint inhibitor, the anti-CTLA-4 antibody ipilimumab (Yervoy), gained FDA approval for patients with unresectable or metastatic melanoma. Since then, antibodies directed at the PD-1/PD-L1 pathway have dominated the field. Research findings that shed light on how best to use these agents in combinations, as well as new checkpoint therapies, are expected this year.

**Drug Development**

Howard A. “Skip” Burris III, MD
Sarah Cannon

Novel therapeutic strategies that are likely to advance this year include expansion of uses for tyrosine kinase inhibitors, new combinations incorporating checkpoint immunotherapy, and progress in developing personalized cancer vaccines, according to Howard A. “Skip” Burris III, MD.

“Across all of oncology, there are several common buckets,” said Burris, chief medical officer and president of clinical operations at Sarah Cannon in Nashville, Tennessee, and a 2014 Giants of Cancer Care® award winner in the Drug Development category. “There is a lot of promise across most of the disease entities from the research that’s been done.”

Molecularly targeted therapies continue to gain traction, some in multiple tumor types, Burris said, citing agents directed at FGFR2, KRAS, and RET activity as examples. “We have seen that with pemigatinib [Pemazyre], the FGFR2 inhibitor, in cholangiocarcinoma, which will certainly play in some other areas. KRAS—the long, undruggable target—has seen the KRAS G12C inhibitors, and we’ve had the approval of the RET inhibitors in lung cancer and thyroid cancer. We are seeing that we no longer have undruggable targets, and we know that we can find driver mutations in small sets of patients; it’s certainly a place to go to pursue development,” he said.

In immunotherapy, clinical findings are starting to emerge for combination therapies involving PD-1/PD-L1 inhibitors, including some regimens that pair immune checkpoint agents, Burris noted. “We’re seeing that combinations with other antibodies, TIGIT and LAG3, are showing improved activity over what seemed to be a checkpoint inhibitor alone, as well as activity in patients who previously had a checkpoint inhibitor, and that’s playing out in tumors as diverse as lung cancer, colon cancer, and melanoma—so really, this is across the spectrum. There’s a lot of excitement there.”

Furthermore, Burris anticipates that CAR T-cell therapies, or other types of genetically modified treatments will move forward in clinical development, including in solid tumor trials. “We’ve got more than a dozen trials ongoing at Sarah Cannon, and patients are being matched to those studies. There’s a great deal of enthusiasm, and I’m
Debu Tripathy, MD, is looking forward to gaining deeper insights into immunotherapy, ADCs, oral formulations of chemotherapy, and AKT inhibitors in breast cancer. “2021 is going to be a refreshing year in many ways, with a lot of new data and advances for our patients with breast cancer,” said Tripathy, a professor and chairman of the Department of Breast Medical Oncology in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston.

Although more data are needed, Tripathy emphasized that findings from the phase 3 CONTESSA trial (NCT03326674) could advance the arena of oral taxane therapy over intravenous options. The combination of tesetaxel, a novel oral taxane, plus a reduced dose of oral capcitabine demonstrated improved outcomes over capcitabine alone in patients with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with a taxane, according to findings presented at the 2020 San Antonio Breast Cancer Symposium. The tesetaxel regimen resulted in median progression-free survival (PFS) of 9.8 months (95% CI, 8.4-12.0) compared with 6.9 months (95% CI, 5.6-8.3) with capcitabine alone (HR, 0.716; 95% CI, 0.573-0.895; P = .003).

Unlike standard paclitaxel and docetaxel, tesetaxel can be orally administered because of its improved bioavailability and resistance to the P-glycoprotein efflux pump, which mediates gastric absorption and chemotherapy resistance. “Because it can be used as a stand-alone regimen, it may make adjuvant and metastatic therapy easier to tolerate,” said Tripathy, adding that the tesetaxel regimen does carry more neuropathy than capcitabine alone. “We could have oral regimens where people don’t even have to come to infusion centers.”

In targeted therapies, Tripathy expects the science to move forward on AKT inhibitors even though 1 agent in this class, ipatasertib, failed to show a significant improvement in PFS in combination with paclitaxel compared with placebo plus paclitaxel in patients with locally advanced or metastatic TNBC. In summary, Tripathy noted, there will be more data from this class of drugs.

For immunotherapy, a constantly evolving field, Tripathy predicted that nearly every medical meeting in 2021 will provide updates. Following the readouts of the IMPassion031 (NCT03197935) and KEYNOTE-355 (NCT02819518) trials, which led to the approvals of atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane) and pembrolizumab (Keytruda) plus chemotherapy in patients with unresectable locally advanced or metastatic PD-L1-positive TNBC, more findings from immunotherapy studies in earlier stages of disease are expected.

“There are trials going on in [hormone receptor]-positive breast cancer in the neoadjuvant setting with pembrolizumab in patients with [stage] III breast cancer, so we’re going to be getting a lot of output from trials in the ones that are in the early-stage setting—which are very important for preventing a recurrence in the first place—if it can be given with good quality of life,” Tripathy said.

We could have oral regimens where people don’t even have to come to infusions centers.” —DEBU TRIPATHY, MD
In the lung cancer field, 2021 will encompass a greater focus on adjuvant trials, additional novel molecular compounds for select patient subgroups, and a migration of circulating tumor DNA (ctDNA) analysis into a more minimal residual disease (MRD)-based setting, according to Balazs Halmos, MD, MS.

“2020, despite being a terrible year as a result of COVID-19, actually has been a good year for thoracic oncology,” said Halmos, a professor of clinical medicine at Albert Einstein College of Medicine and director of both the Multidisciplinary Thoracic Oncology Program and Clinical Cancer Genomics at Montefiore Medical Center, both in Bronx, New York. “As for next year, I think it will be hard to replicate what we’ve seen this year in terms of the great successes, but there are definitely a number of stories that will continue to unfold.”

The KRAS story, a molecular target long considered undruggable, is certainly an area where advances will continue, Halmos predicted. The agent that has attracted the most attention in this category so far is sotorasib (formerly AMG 510), a KRAS inhibitor being developed under a breakthrough therapy designation for patients with locally advanced or metastatic NSCLC with KRAS G12C mutations.

In the phase 2 CodeBreaK100 study (NCT03600883), sotorasib demonstrated an ORR of 32.2% (95% CI, 20.62%-45.64%) among previously treated patients with mutated NSCLC. Studies of other KRAS pathway inhibitors are under way, and Halmos said next steps will include combining these agents in the first-line setting with chemotherapy and/or immunotherapy. “There are some of the downstream inhibitors—for example, the SOX-inhibiting compounds—so there is great excitement in that field,” he said.

Other targets of interest that will gain more traction this year include therapies aimed at EGFR exon 20 insertion and HER2 (ERBB2), as data sets continue to mature and results are reported. The challenge, Halmos said, will be to identify which patient subgroups are the best candidates to receive novel ADCs such as trastuzumab deruxtecan and patritumab deruxtecan (U3-1402), which have demonstrated anti-tumor activity in HER2-expressing or HER2-mutant and HER3-expressing/EGFR-mutant NSCLC, respectively.

“ERBB2 is emerging as a real target now in lung cancer with these excellent antibody-drug conjugates that have shown success in breast, colon, and gastric cancers and likely will yield great benefits in ERBB2-positive lung cancer patients, as well,” Halmos said.

In immunotherapy, Halmos is hoping for further advances in the adjuvant setting, both as monotherapy and in combination, for stage III disease. The phase 3 PACIFIC trial (NCT02125461), which led to the approval of the PD-L1 inhibitor durvalumab (Imfinzi) for patients with unresectable stage III NSCLC, initiated a new journey for checkpoint inhibitors as adjuvant therapy. “In PACIFIC, we’ve seen a major advance, but why not take another step forward?” Halmos said.

As for new molecules, tiragolumab, a monoclonal antibody directed at the TIGIT inhibitory immune checkpoint, is part of a new wave of developing strategies to leverage the immune system for anticancer therapy. These include vaccines that expand lymphocytes. “It can also be a more individualized approach; it’s almost like the CAR T-cell therapy approaches that are being investigated in some of these particular subsets,” Halmos said. “There is a lot of excitement there.”

Anticipation is also building with canakinumab (Ilaris), which is currently indicated for the treatment of a spectrum of autoinflammatory conditions, such as rheumatologic disorders. The agent demonstrated tolerability when used in combination with pembrolizumab and platinum-based doublet chemotherapy in the phase 2 CANOPY-1 trial (NCT03631199) in patients with advanced or metastatic NSCLC.

In addition to therapeutic changes, Halmos is anticipating growing clinical utility for ctDNA assays. Given their convenience and ease, Halmos emphasized, practitioners should already be familiar with utilizing ctDNA testing to make individualized treatment decisions for patients with lung cancer. However, he is ready for the technology to move to the next level.

“I’m very eager to see ctDNA moving into the MRD platforms, where we can detect MRD after surgery or definitive chemoradiation and can use it to monitor immunotherapy responses. We’ve seen a lot of exciting technologies this year reflecting that, so that’s the next wave,” Halmos said.

Major developments that unfolded in late 2020 will shape practice and research for prostate, bladder, and kidney cancers going forward, said Neeraj Agarwal, MD. He is a professor of medicine and holds a Presidential endowed chair of cancer research at the University of Utah Huntsman Cancer Institute (HCI). He also serves as director of the Genitourinary Oncology Program and the Center of Investigational Therapeutics, and coleads the Experimental Therapeutic Program at the HCI.

Agarwal called the FDA approvals of the PARP inhibitors olaparib (Lynparza) and rucaparib (Rubraca) the biggest highlight in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) in 2020. Rucaparib is indicated for men with a deleterious BRCA1 mutation (germline and/or somatic) who have been treated with a novel androgen signaling-directed therapy and a taxane-based chemotherapy. Olaparib is approved for men with multiple deleterious or suspected deleterious germline or somatic homologous recombination repair gene mutations including BRCA1 and BRCA2 who have progressed following prior treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga).

“We are going to see movement of PARP inhibitors to earlier lines of therapies with 3 trials going on in the first-line mCRPC
Looking Forward

**TABLE. Select Phase 3 Trials of First-line PARP Inhibitors for mCRPC**

<table>
<thead>
<tr>
<th>Trial name (ClinicalTrials.gov identifier)</th>
<th>Experimental Intervention</th>
<th>Primary outcome</th>
<th>Estimated enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TALAPRO-2 (NCT03395197)</td>
<td>Talazoparib plus enzalutamide</td>
<td>rPFS</td>
<td>1037</td>
</tr>
<tr>
<td>MAGNITUDE (NCT03748641)</td>
<td>Niraparib plus abiraterone and prednisone</td>
<td>rPFS</td>
<td>1000</td>
</tr>
<tr>
<td>PROpel (NCT03732820)</td>
<td>Olaparib plus abiraterone</td>
<td>rPFS</td>
<td>720</td>
</tr>
</tbody>
</table>

mCRPC, metastatic castration-resistant prostate cancer; rPFS, radiographic progression-free survival.

setting, which will be declaring results in 2021 or 2022,” Agarwal said. These studies, all phase 3 trials, are TALAPRO-2 (NCT03395197), testing talazoparib (Talzenna) plus enzalutamide; MAGNITUDE (NCT03748641), evaluating niraparib (Zejula) plus abiraterone and prednisone; and PROpel (NCT03732820), exploring olaparib plus abiraterone (TABLE). In advanced bladder cancer, results from the JAVELIN Bladder 100 trial (NCT02603432) published in September established maintenance avelumab (Bavencio), as the standard of care. Maintenance avelumab plus best supportive care (BSC) induced a median overall survival of 21.4 months (95% CI, 18.9-26.1) compared with 14.3 months (95% CI, 12.9-17.9) for BSC alone (HR for death, 0.69; 95% CI, 0.56-0.86; P = .001). At 1 year, 71.3% of patients in the experimental arm were alive versus 58.4% of those in the BSC arm. Patients in the trial had unresectable locally advanced or metastatic urothelial carcinoma without disease progression after 4 to 6 cycles of platinum-based chemotherapy.11

The finding “undoubtedly places avelumab as the treatment of choice with category 1 evidence endorsed by all major guidelines,” Agarwal said. “I don’t think we have seen a similar magnitude of survival benefit with any treatment ever in the setting of metastatic bladder cancer.”

In 2021, Agarwal expects the ADCs enfortumab vedotin-efjv (Padcev) and sacituzumab govitacan to be important developing agents. “We will see various combinations of these drugs coming up,” Agarwal said. “The phase 3 trial [EV-302; NCT04223856] has already started in the first-line setting, where enfortumab vedotin is being combined with pembrolizumab, and I think similar trials of sacituzumab are expected down the line,” he said. “This will mean that this highly well-tolerated chemotherapy delivering ADCs will be available to our patients who are newly diagnosed with metastatic bladder cancer in the very near future; I’m really hoping in the next few years at most.”

In metastatic renal cell carcinoma (RCC), Agarwal expects a new class of drugs, hypoxia-inducible factor-2a (HIF-2a) inhibitors, to become “a huge story.” In July 2020, the FDA granted breakthrough therapy designation to MK-6482 for the treatment of patients with von Hippel-Lindau (VHL) disease-associated RCC with nonmetastatic tumors less than 3 cm who do not require immediate surgery. The agency also granted the HIF-2a inhibitor orphan drug designation for patients with VHL disease.12

Investigators are exploring the novel agent azipladi (Tivozanib), which is a VEGF inhibitor, in a phase 3 trial (NCT04195750) in advanced RCC, and a phase 1/2 dose-escalation and dose-expansion trial (NCT02974738) in advanced solid tumors, including advanced RCC.

Development of established agents will continue as well, Agarwal added. “We will be seeing the field of metastatic RCC rapidly evolving in 2021, with approval of cabozantinib [Cabometyx] with nivolumab [Opdivo], approval of pembrolizumab plus lenvatinib [Lenvima], and newer trials testing HIF-2a inhibitors in various combinations and, hopefully, approval of HIF-2a inhibitors for our patients.”

HEMATOLOGIC MALIGNANCIES

Cellular and targeted therapies continued to dominate the trends in the treatment of hematologic malignancies last year. Although practice-changing data did not shake up the treatment landscape dramatically in 2020, research presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition set the stage for where the field is headed in 2021, according to Lori A. Leslie, MD.

“I’m very hopeful that we will gain more data about how to individualize treatment using targeted therapies in a way that we’re able to offer time-limited rather than indefinite therapy, hopefully for all patients,” said Leslie, director of indolent lymphoma and chronic lymphocytic leukemia research programs at Hackensack Meridian Health John Theurer Cancer Center and assistant professor at Hackensack Meridian School of Medicine in New Jersey.

Progress with CAR T-cell therapy has continued; however, despite success in certain patients, efforts to increase response rates and reduce relapse rates have been an ongoing focus of research. Other strategies garnering attention across hematologic malignancies include the development of next-generation CAR constructs such as dual-targeting of CD20 and CD3, combination therapy with immune checkpoint inhibitors, and the identification of high-risk patients prior to induction therapy.

“I’m most excited about CAR T-cell therapy as well as bispecific antibody therapies. We’ve seen a lot of data at 2020 ASH, including those from ZUMA-5, which looked at CD19 CAR T-cell therapy in patients with relapsed/refractory follicular lymphoma or marginal zone lymphoma [and] showed a high overall response rate,” Leslie said.

In updated data from ZUMA-5 (NCT03105336), axicabtagene ciloleucel (Yescarta) had an ORR by independent radiology review committee of 92% (95% CI, 85%-97%), with a complete response (CR) rate of 76% (95% CI, 67%-84%) and a partial response (PR) rate of 16% in patients with indolent non-Hodgkin lymphoma.13 In patients with follicular lymphoma, the ORR was 94%, with a CR rate of 80% and a PR rate of 14%. Leslie cited these data as hopeful, adding, “This will transform how we treat relapsed/refractory follicular lymphoma, at least in the near future.”

In the area of bispecific T-cell engagers,
Looking Forward

data from several phase 1 trials were presented, including findings for mosunetuzumab and glofitamab, designed to target CD20 on the surface of B cells and CD3 on the surface of T cells, respectively. Data from the phase 1/1b GO29781 study (NCT02500407) in relapsed/refractory follicular lymphoma showed a 51.6% CR rate among 62 patients treated with mosunetuzumab. Further, glofitamab elicited a 53.6% CR rate in 28 patients with aggressive non-Hodgkin lymphoma in the phase 1/1b NP30179 study (NCT03075696). I think in 2021 we should certainly keep our eyes open for more data on bispecific antibodies in certain hematologic malignancies, Leslie said.

Investigators are also focusing on combining agents with nonoverlapping toxicity profiles that have demonstrated synergy in preclinical settings. “We have a number of single agents [that have] modest activity, but are easy to tolerate,” Leslie said. “And we will continue to learn how to rationally combine them moving forward, particularly in relapsed/refractory indolent lymphomas.” Leslie cited the results from the phase 1/2 trial (NCT02956382) of ibrutinib (Imbruvica) and venetoclax (Venclexta) in patients with relapsed/refractory follicular lymphoma.

As monotherapy, the Bruton tyrosine inhibitor and the BCL2 inhibitor have response rates of approximately 20% and 38%, respectively, according to Leslie. When administered at the phase 2 recommended dose of 560-mg ibrutinib with 600-mg venetoclax, the response rate was 83% with a CR rate of 33% (n = 6).

I’m hopeful that we’ll be shifting toward a personalized, molecularly driven combination nonchemotherapy approach for more patients with relapsed/refractory indolent lymphomas,” Leslie said.

However, an area of study that deserves attention in the clinic moving forward is the importance of checking patients for high-risk features before the initiation of therapy, especially in patients with chronic lymphocytic leukemia (CLL). “[Evaluating patients for these features] has not only prognostic value in terms of telling the patient how you expect them to respond to therapy, but it also has significant predictive value in that it can help with treatment selection and patients with high risk,” Leslie said. “For example, patients with CLL really should not be treated with chemoimmunotherapy outside extenuating circumstances.”

Data from a real-world study, presented by Leslie at 2020 ASH, compared clinical outcomes in patients with high-risk CLL who received first-line ibrutinib versus those who received chemoimmunotherapy. In the retrospective analysis, patients were defined as high risk if their disease harbored a 17p deletion (del), del(11q), a TP53 mutation, or an unmutated IGHV, or a complex karyotype of 3 or more chromosomal abnormalities.

Of the 516 patients included in the analysis, which spanned 40 treatment sites in the United States, 271 were identified as having high-risk CLL, of whom 175 received ibrutinib and 96 received chemoimmunotherapy. Time to next treatment (TTNT) was used as a surrogate end point for PFS and was significantly longer in those treated with ibrutinib, with a median TTNT not yet reached compared with 34.4 months with chemoimmunotherapy (HR, 0.46; 95% CI, 0.34-0.62; P < .01).

“Another way to look at longer-term outcomes was looking at the number of patients who required only 1 line of therapy during the study period,” said Leslie. “For those on ibrutinib, 74.7% needed only 1 line of therapy compared with 47.0% of patients treated with chemoimmunotherapy. The remainder of those treated with chemoimmunotherapy went on to a second line of therapy. Treating patients with targeted therapy in some way at least partially neutralizes the poor prognostic indication or implication of a TP53 abnormality or a mutated IGHV.”

Gina Mauro, editorial director of oncology for OncLive®, and senior editors Jason Harris and Brittany Lovely contributed to this report.

For a full list of references, see the article at OncLive.com.
Join Ajai Chari, MD, to learn more about recent advancements in the oncology treatment landscape with this iPub® on immuno-oncology and the Bispecific T-Cell Engager (BiTE®) technology, a novel targeted immuno-oncology platform.¹ BiTE® molecules are designed to engage the cytotoxic potential of the body’s endogenous T cells to various tumor-specific antigens to target and help eliminate detectable cancer cells.²,³

In this iPub®, Dr Chari will highlight the targets of some of the investigational BiTE® molecules, including B-cell maturation antigen in multiple myeloma and prostate-specific membrane antigen in prostate cancer, as well as other emerging targets in the BiTE® immuno-oncology platform.⁴

**References**

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Asciminib Boosts Major Molecular Response in Pretreated, Chronic-Phase CML

by GINA MAURO

ASCIMINIB, A SMALL MOLECULE with a novel mechanism for inhibiting ABL, demonstrated a statistically significant and clinically meaningful improvement in the major molecular response (MMR) rate at 24 weeks compared with bosutinib (Bosulif) in patients with previously treated chronic myeloid leukemia (CML) in chronic phase (CP), according to findings presented during the 62nd American Society of Hematology Annual Meeting & Exposition (ASH 2020).¹

Results from the phase 3 ASCEMBL study (NCT03106779) showed that the MMR rate was 25.5% with asciminib compared with 13.2% with bosutinib; the common risk difference for MMR was 12.2%, which was found to be statistically significant (95% CI, 2.19%-22.3%; 2-sided \( P = .029 \)) (FIGURE¹).

“Asciminib demonstrated statistically significant superior efficacy compared with bosutinib and a favorable safety profile,” lead study author Andreas Hochhaus, MD, director of the Department of Hematology and Internal Oncology and vice dean for research at University Hospital in Jena, Germany, said in a press briefing during the meeting. “The ASCEMBL data support the use of asciminib as a new treatment option in CML, particularly in patients with resistance or intolerance to at least 2 [tyrosine kinase inhibitors].”

Current therapies for patients who have resistance or intolerance to 2 or more tyrosine kinase inhibitors (TKIs) are limited due to modest efficacy and/or safety concerns. Although ponatinib (Iclusig) is an effective therapy in previously treated patients, it is also linked with increased cardiovascular risk, Hochhaus said. Bosutinib is a second-generation TKI with efficacy in patients with CML who have received at least 2 TKIs.

Asciminib is a first-in-class inhibitor specifically targeting the ABL myristoyl pocket (STAMP), Hochhaus said during his presentation. By contrast, bosutinib and other TKIs target the adenosine triphosphate (ATP) binding site. In August 2020, Novartis, the manufacturer of asciminib, announced that the FDA had granted the STAMP inhibitor a fast track designation.²

**KEY DATA IN THE ASCEMBL TRIAL**

In ASCEMBL, investigators sought to determine the efficacy and safety of asciminib versus bosutinib in 233 patients with CP CML who had received at least 2 prior TKIs. Patients were randomized 2:1 to receive asciminib at 40 mg twice daily (\( n = 157 \)) or bosutinib at 500 mg once daily (\( n = 76 \)) for at least 96 weeks. Patients were stratified by major cytogenetic response (MCyR) status at baseline.

Based on an amendment to the study protocol, switching to asciminib was permitted only for patients who met treatment failure criteria on bosutinib. In all, 28.9% of patients in the bosutinib arm crossed over to asciminib.

To be eligible for enrollment, previously treated patients with CP CML must have received 2 or more TKIs, could not harbor T3151 or V299L point mutations, and had failed or were intolerant to their most recent TKI, and those with intolerance must have had \( BCR-ABL1 \) transcript levels greater than 0.1% at screening.

The primary end point of the trial was MMR rate at 24 weeks while on study treatment without meeting any treatment failure criteria before 24 weeks. Secondary end points included MMR rate at 96 weeks while on study treatment without meeting any treatment failure criteria before 96 weeks,
safety and tolerability, and complete cytogenetic response (CCyR) and MMR rates at and by scheduled data collection time points, time to and duration of MMR, time to and duration of CCyR, time to treatment failure, progression-free survival, overall survival, and pharmacologic parameters.

The data cutoff date was May 25, 2020, at which point all patients completed their week 24 visit or had previously discontinued treatment.

The median age was 52.0 years (range, 19-83), and 51.5% of patients were female. MCyRs had occurred in 29.3% of patients. Patients discontinued their last TKI due to lack of efficacy (63.9%), lack of tolerability (34.8%), or other (1.3%). Patients had received either 2 (48.1%) or 3 or more (51.9%) lines of therapy. Fewer patients in the asciminib arm had detectable BCR-ABL1 mutations at study entry (12.7%) compared with those in the bosutinib arm (17.1%).

At the time of data cutoff, treatment was ongoing in 61.8% of patients on asciminib versus 30.3% of patients on bosutinib. In the asciminib arm and bosutinib arms, patients discontinued treatment due to lack of efficacy (21.0% vs 31.6%, respectively), adverse event (AE; 5.1% vs 21.1%), physician decision (6.4% vs 7.9%), patient decision (2.5% vs 3.9%), death (0.6% vs 0%), lost to follow-up (0.6% vs 1.3%), progressive disease (0.6% vs 3.9%), or protocol deviation (0.6% vs 0%). Twenty-two patients (28.9%) had switched over from bosutinib to receive asciminib.

At a median follow-up of 14.9 months, the median duration of exposure was 43.4 weeks (range, 0.1-129.9) for asciminib and 28.2 weeks (range, 1.0-117.0) for bosutinib. The MMR benefit was observed across key patient subgroups, with a risk difference of 17.3% (95% CI, 3.62-31.0%).

Moreover, the probability of achieving MMR by 24 weeks was 25.0% with asciminib compared with 11.9% with bosutinib, with a cumulative difference between the 2 arms becoming evident around 12 weeks, according to Hochhaus. The rate of CCyR at 24 weeks was 40.8% and 24.2% with asciminib and bosutinib, respectively, with a common risk difference of 17.3% (95% CI, 3.62-31.0%).

Data also showed that the deep molecular response of MR4 at 24 weeks was 10.8% and 5.3% with asciminib and bosutinib, respectively. These rates were 8.9% and 1.3% for MR4.5. For patients who had BCR-ABL1% of 1% or more at baseline, transcript levels dropped to 1% or less at week 24 for 44.5% treated with asciminib compared with 22.2% who received bosutinib.

**SAFETY FINDINGS**

Regarding safety, all-grade and grade 3 or higher AEs were similar between arms (all-grade, 89.7% with asciminib vs 96.1% with bosutinib; grade ≥ 3, 50.6% vs 60.5%, respectively). Two deaths occurred on the asciminib arm due to arterial embolism and ischemic stroke (n = 1 each), which were not considered related to study treatment, and 1 on the bosutinib arm due to septic shock after disease progression. Two additional patients who were randomized to asciminib died during survival follow-up due to CML.

Overall, 5.8% of patients who received asciminib and 21.1% of those who received bosutinib discontinued treatment due to AEs. The most common AEs that led to asciminib discontinuation included thrombocytopenia (3.2%) and neutropenia (2.6%); for bosutinib discontinuation included increased alanine aminotransferase (ALT; 5.3%) and increased aspartate aminotransferase (AST; 2.6%).

All-grade and grade 3 or higher AEs that led to dose adjustments/interruptions occurred in 37.8% and 34.0% of patients on asciminib, respectively, and 60.5% and 48.7% on bosutinib. All-grade AEs that required additional therapy occurred in 66.0% of patients on asciminib and 88.2% of those on bosutinib; grade 3 or higher AEs that led to additional therapy occurred in 28.2% and 40.8% of patients, respectively.

The most frequent all-grade AEs occurring in at least 20% of patients receiving asciminib compared with bosutinib were, respectively, thrombocytopenia (28.8% vs 18.4%), neutropenia (21.8% vs 21.1%), diarrhea (11.5% vs 71.1%), nausea (11.5% vs 46.1%), rash (7.1% vs 23.7%), vomiting (7.1% vs 26.3%), increased ALT (3.8% vs 27.6%), and increased AST (3.8% vs 21.1%).

Arterial-occlusive events occurred in 5 patients (3.2%) on asciminib: 2 cases of myocardial ischemia and 1 each of coronary artery disease, ischemic stroke, and mesenteric embolism/thrombosis. One patient (1.3%) on bosutinib experienced an arterial-occlusive event involving acute coronary syndrome.
Patients on asciminib with mutations at baseline also developed newly emerging BCR-ABL1 mutations; these occurred at the ATP binding site (n = 3). In participants without mutations at baseline who received asciminib, mutations emerged at the ATP binding site (n = 2) and at the myristoyl binding pocket (n = 2). No patients on bosutinib had newly emerging mutations. However, Hochhaus said, “conclusions on the impact of mutations cannot be made, due to their low incidence and heterogeneity.”

During the press briefing, Hochhaus noted that Novartis is planning to submit regulatory applications for approval of asciminib to the FDA and European Medicines Agency in early 2021. Investigators also plan to evaluate asciminib in earlier lines of therapy for CML. “Third-line treatment will not be the only indication for asciminib, but it will certainly be the first indication for this drug,” Hochhaus said. “My personal expectation is that first-line response [to asciminib] will be even stronger, even better.”

The ongoing, 4-arm, phase 2 CMLXI trial (NCT03906292) is evaluating the combination of asciminib with various TKIs in the frontline setting of patients with CP CML. In the study, asciminib is administered at varying daily doses (40 mg, 60 mg, and 80 mg) and at a twice-daily 20-mg dose in combination with imatinib (Gleevec), nilotinib (Tasigna), or dasatinib (Sprycel). For a full list of references, see the article at https://bit.ly/373FIVu.

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**Novel Combo Outperforms Chemoimmunotherapy in CLL**

**by BRITTANY LOVELY**

THE COMBINATION OF UBLITUXIMAB and umbralisib (U2), 2 investigational compounds with different targets, significantly improved progression-free survival (PFS) in patients with chronic lymphocytic leukemia (CLL) compared with obinutuzumab (Gazyva) plus chlorambucil irrespective of prior treatment, according to results from the phase 3 UNITY-CLL study (NCT02612311) presented at ASH 2020.

At a median follow-up of 36.7 months, U2 improved median PFS versus chemoimmunotherapy across subgroups. In the intention-to-treat population, the median PFS was 31.9 months (95% CI, 28.2-35.8) with U2 versus 17.9 months (95% CI, 16.1-22.6) with standard of care (HR, 0.546; 95% CI, 0.413-0.720; P < .001). The 24-month PFS rates were 60.8% and 40.4%, respectively. In patients who were treatment naïve at the time of enrollment, the median PFS was 38.5 months (95% CI, 33.2-43.2) with U2 compared with 26.1 months (95% CI, 19.4-33.1) with the obinutuzumab combination (HR, 0.482; 95% CI, 0.316-0.736; P < .001). The 24-month PFS rates were 76.6% and 52.1%, respectively.

The U2 regimen would represent a new targeted therapy option in the CLL paradigm. Ublituximab, a monoclonal antibody, targets a unique isoform of CD20, whereas umbralisib selectively inhibits PI3Kδ and CK-1ε, said global study chair John G. Gribben, DSc, FRCP, FRCPath, FMedSci, in presenting the data. Gribben is a professor of experimental cancer medicine and director of both the Experimental Cancer Medicine Centre and Stem Cell Transplantation at Saint Bartholomew’s Hospital, Queen Mary’s School of Medicine, at the University of London in England.

“Bruton tyrosine kinase [BTK] and BCL-2 inhibitors have dramatically changed the therapeutic landscape of CLL, but not all patients are candidates for these agents, and mechanisms of resistance have already been identified,” Gribben said. “I think PI3Kδ inhibitors offer a distinct mechanism of action from all the BTK and BCL-2 inhibitors and have demonstrated promising activity in the relapsed/refractory CLL setting.”

In addition to its efficacy, the U2 regimen has a favorable safety profile and exhibited low rates of immune-mediated toxicities that are typically associated with other PI3Kδ inhibitors, including diarrhea, colitis, pneumonia, and hepatic toxicity. In previously untreated patients these toxicities lead to discontinuation rates of greater than 50%.

In total, 421 patients with treatment-naïve or relapsed/refractory CLL were included in the primary analysis of the UNITY-CLL trial; 57% of patients were treatment naïve and 43% had relapsed/refractory CLL.

Umbralisib was given orally at 800 mg once daily until progression or treatment discontinuation. Ublituximab was administered intravenously at 900 mg on days 1/2 (150 mg on day 1 followed by 750 mg on day 2), 8, and 15 of cycle 1; day 1 of cycles 2 to 6, and on day 1 every 3 cycles after cycle 6. Obinutuzumab, which also is a CD20-directed antibody, was given intravenously at 1000 mg on days 1/2 (100 mg on day 1 followed by 900 mg on day 2), 8, and 15 of cycle 1; day 1 of cycles 2 to 6. Chlorambucil was given orally at 0.5 mg/kg on day 1 and 15 of cycles 1 to 6. Each cycle was 28 days.

The primary end point was independent review committee (IRC)-assessed PFS and key secondary end points included IRC-assessed overall response rate (ORR), complete response (CR), and safety assessed from the first dose until 30 days after the last dose.

The ORR for 210 patients treated in the U2 cohort was 83.3% compared with 68.7% for the 211 patients in the obinutuzumab arm (P < .001). Of the responders, 5% achieved a CR or CR with incomplete marrow recovery and 79% had a partial response with U2 versus 1% and 67%, respectively, with the obinutuzumab combination.

In stratified analysis, the ORRs were 84%, 82%, and 57% for patients in the U2 cohort who were treatment naïve, were previously treated, and had prior treatment with...
Axi-cel Generates 92% ORR in Indolent Non-Hodgkin Lymphoma

by GINA MAURO

AXICABTAGENE CILOLEUCEL (axi-cel; Yescarta) demonstrated high rates of durable responses in patients with indolent non-Hodgkin lymphoma (NHL), according to extended follow-up results of the ZUMA-5 trial presented during ASH 2020.1

At a median follow-up of 17.5 months, the objective response rate (ORR) by independent radiology review committee (IRRC) was 92% (95% CI, 85%-97%), with a complete response (CR) rate of 76% (95% CI, 67%-84%). Further, the partial response (PR) rate was 16%, stable disease (SD) was reported in 3% of patients, and 5% were undefined.

Specifically, in 84 patients with follicular lymphoma, the ORR was 94%, with a CR rate of 80% and a PR rate of 14%. Four percent of patients had SD and 2% were undefined. In those with marginal zone lymphoma (MZL; n = 20), the ORR was 85%, with a CR rate of 60% and a PR rate of 25%; zero patients had SD, and 15% of patients were undefined.

“Axi-cel may be a highly promising therapeutic approach for patients with relapsed/refractory indolent NHL,” said lead study author Caron A. Jacobson, MD, MMSc, medical director of the Immune Effector Cell Therapy Program and a senior physician at Dana-Farber Cancer Institute and an assistant professor of medicine at Harvard Medical School, both in Boston, Massachusetts. “Given the long natural history of these diseases, safety is of paramount importance. The safety profile was manageable and reversible and appeared to be at least similar to that of axi-cel in aggressive lymphomas. This may have implications for the possibility of outpatient therapy, and evaluation of this is planned.”

Patients with advanced-stage indolent NHL, including follicular lymphoma and MZL, frequently relapse on standard treatment, and remission durations for these patients shorten with subsequent lines of therapy.

Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of adult patients with relapsed/refractory large B-cell lymphoma following 2 or more lines of systemic treatment based on findings from the ZUMA-1 trial (NCT02348216). Updated data from the trial showed that axi-cel elicited an ORR of 83% in the modified intent-to-treat population, and a 58% CR rate.2

In the multicenter, single-arm, phase 2 ZUMA-5 trial (NCT03105336), investigators sought to evaluate axi-cel in patients with relapsed/refractory indolent NHL, either follicular lymphoma or MZL, following 2 or more lines of therapy. A total 151 patients were enrolled, and 146 patients were treated as of the March 12, 2020, data cutoff and had either follicular lymphoma (n = 124) or MZL (n = 22).1 The MZL cohort was exploratory, and all analyses for this cohort were descriptive in nature, Jacobson noted.

To be eligible for enrollment, patients needed to have relapsed/refractory follicular lymphoma in grades 1 to 3A or MZL that was nodal or extranodal. Patients must have received 2 or more prior lines of treatment that included an anti-CD20 monoclonal antibody plus an alkylating agent. Conditioning regimens included intravenous (IV) fludarabine (30 mg/m²) and IV cyclophosphamide (500 mg/m²) on days −5, −4, and −3. Axi-cel was manufactured for all 151 enrolled patients and was delivered to the study site a median 17 days following leukapheresis. It was administered at 2 x 10⁶ CAR+ cells/kg.

The primary end point of the trial was IRRC-assessed ORR per Lugano classification. Secondary end points included IRRC-assessed CR rate, investigator-assessed ORR, duration of response (DOR), progression-free survival (PFS), overall survival (OS), adverse effects (AEs), and CAR T-cell and cytokine levels.
The efficacy analyses included 104 patients: those with follicular lymphoma who had at least 1 year of follow-up (n = 84) and patients with MZL with at least 4 weeks of follow-up (n = 20).

Overall, the median age was 61 years (range, 34-79), and 35% of patients were 65 years or older. Fifty-seven patients had at least 4 weeks and patients with MZL with at least 1 year of follow-up (n = 84). Those with follicular lymphoma who had a CR and PR had a median DOR of 10.6 months and 8.1 months, respectively; the 1-year DOR rates were NE and 0%, respectively. However, Jacobson noted that the follow-up for the MZL cohort was much more limited, making these DOR data immature.

Moreover, further findings showed that the median PFS was NE (95% CI, 23.5-NE), and the 1-year PFS rate was 73.7%. In patients with follicular lymphoma, the median PFS was NE and the 12-month PFS rate was 77.5%; in patients with MZL, the median PFS was 11.8 months and the 1-year PFS rate was 45.1%.

The median OS in all patients was NE, and the 1-year OS rates for the overall population, those with follicular lymphoma, and those with MZL were 92.9%, 92.8%, and 92.9%, respectively.

The median follow-up for the safety analysis was 15.1 months (range, 0.5-31.6) and included all 146 patients. Grade 3 or higher AEs occurred in 86% of patients, the most common of which were cytopenias (70%) and infections (16%). Three deaths were reported: 1 axi-cel-related because of multisystem organ failure in the context of cytokine release syndrome (CRS; day 7), and the other 2 were unrelated to study treatment and due to aortic dissection (1 on day 399) and coccidiodomycosis (1 on day 327).

Overall, 82% of patients experienced any-grade CRS, and 7% had grade 3 or higher CRS. Ninety-six percent of patients experienced pyrexia, and 41% had hypertension. Moreover, approximately half (49%) had their AEs managed with tocilizumab, and 17% received corticosteroids. Grade 4/5 CRS occurred in 1 patient each, and no patients had ongoing CRS as of the cutoff date.

The median time to onset of CRS was 4 days (range, 1-15), and the median duration of events was 6 days (range, 1-27). Ninety-nine percent of patients, however, had resolved events.

The overall incidence of any-grade and grade 3 and higher neurologic events were 60% and 19%, respectively. Tremor and confusional state occurred in 52% and 40% of patients, respectively. To manage these AEs, 36% of patients received corticosteroids and 6% were given tocilizumab.

When stratified by cohort, patients with MZL had higher rates of grade 3 or higher neurologic events versus those with follicular lymphoma (41% vs 15%, respectively). Grade 4 neurologic events occurred in 3 patients, and no grade 5 events were reported.

The median time to peak of anti-CD19 CAR T-cell levels after the infusion of axi-cel was 9 days (range, 8-371). The CAR T-cell expansion and outcomes were compared with data in more aggressive lymphoma subtypes. CAR T-cell expansion and outcomes were seen in patients with MZL.

In a press briefing during the meeting, Jacobson suggested that the biology of indolent NHL could be a reason for the higher efficacy rates and more tolerable safety profile with axi-cel compared with data in more aggressive lymphoma subtypes.

“It is the disease biology itself. We know that each of these lymphomas have unique microenvironments that may or may not make them more susceptible to immunologic killing,” Jacobson explained. “We know follicular lymphoma is a disease that can be cured by allogeneic stem cell transplant to a larger degree than what is seen with aggressive B-cell non-Hodgkin lymphomas. That may, in part, explain the efficacy.”

For a full list of references, see the article at https://bit.ly/3m8AIhK.
A FOUNDATION in MM maintenance therapy post auto-HSCT

Lenalidomide (REVLIMID)

- The ONLY preferred National Comprehensive Cancer Network® (NCCN®) Category 1 maintenance therapy post auto-HSCT
- The ONLY FDA-approved maintenance therapy post auto-HSCT
- The #1 prescribed maintenance therapy post auto-HSCT

Indications

REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Selected Safety Information: Boxed WARNINGS

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

See the next spread and Brief Summary for complete Boxed WARNINGS.

EMBRYO-FETAL TOXICITY

- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS® program.

HEMATOLOGIC TOXICITY

- REVLIMID can cause significant neutropenia and thrombocytopenia.

VENOUS AND ARTERIAL THROMBOEMBOLISM

- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dexamethasone. Anti-thrombotic prophylaxis is recommended.

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. 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 risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

Please see Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
5.7-year median PFS with REVLIMID Maintenance²

3.8 YEAR INCREASE IN MEDIAN PFS VS PLACEBO (UPDATED ANALYSIS: MARCH 2015)†

CALGB PFS Events: REVLIMID = 97/231 (42%), Placebo = 116/229 (51%)
IFM PFS Events: REVLIMID = 191/307 (62%), Placebo = 248/307 (81%)

5.7 years
(95% CI 4.4, NE)

1.9 years
(95% CI 1.6, 2.5)

IFM (Study 2): 1.9-year advantage in median PFS vs placebo†

Median PFS: 3.9 years with REVLIMID Maintenance (95% CI 3.3, 4.7) (n=307) vs 2.0 years with placebo (95% CI 1.8, 2.3) (n=307) (HR 0.53 [95% CI 0.44, 0.64])

Trial design: CALGB (Study 1) and IFM (Study 2) were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies in newly diagnosed patients 18-70 years (CALGB) and <65 years at diagnosis (IFM) who received auto-HSCT following induction therapy, which must have occurred within 12 months. Patients were randomized 1:1 to receive REVLIMID or placebo maintenance 90-100 days (CALGB) or within 6 months (IFM) post auto-HSCT. Patients were required to achieve at least stable disease following hematologic recovery and CrCl ≥30 mL/min. The primary endpoint for both studies was PFS, based on assessment by investigator, and was defined from randomization to the date of progression or death, whichever occurred first. In both studies, the starting dose of REVLIMID was 10 mg once daily for repeated 28-day cycles. After 3 months, a dose increase to 15 mg once daily occurred in 135 patients (58%) in CALGB, and 185 patients (60%) in IFM. The dose was reduced, interrupted, and/or discontinued as needed to manage toxicity. Patients were treated until disease progression, unacceptable toxicity, or patient withdrawal for any reason. At a preplanned interim analysis, the primary endpoint of PFS was met and both studies were unblinded, and patients continued to be followed as before. Patients in the placebo arm of CALGB were allowed to cross over to receive REVLIMID before disease progression; patients in the IFM study were not recommended to cross over. In IFM, REVLIMID was stopped at the recommendation of the Data Monitoring Committee in January 2011.

*See full NCCN Clinical Practice Guidelines In Oncology* (NCCN Guidelines*) for further detail about recommended therapies.
‡Updated analysis, March 2015. Based on intent-to-treat (ITT) population.
auto-HSCT, autologous hematopoietic stem cell transplantation; CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; IFM, Intergroupe Francophone du Myélome; MM, multiple myeloma; NE, not evaluable; PFS, progression-free survival.
Indications

REVLIMID® (lenalidomide) is indicated as maintenance therapy in adult patients with multiple myeloma (MM) following autologous hematopoietic stem cell transplantation (auto-HSCT). REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity
Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program.

Information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)
REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous and Arterial Thromboembolism
REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient’s underlying risks.

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. 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 risk to the fetus.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS

Females of Reproductive Potential: See Boxed WARNINGS.

Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.

Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
B:11.25" FS:7"

A decrease in the number of CD34+ cells collected after treatment is (65 Medium) with REVLIMID and high WBC at baseline (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize recommended to withhold treatment with REVLIMID until TFR resolves to ≤ lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL.

Tumor Lysis Syndrome (TLS): (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Increased Mortality With Pembrolizumab: In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID + dexamethasone. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Severe Cutaneous Reactions: Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

Tumor Lysis Syndrome (TLS): Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

Tumor Flare Reaction (TFR): TFR has occurred during investigational use of REVLIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion.

Impaired Stem Cell Mobilization: A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before starting REVLIMID treatment and during therapy.

Early Mortality in Patients With MCL: In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥10 x 10⁹/L).

Hypersensitivity: Hypersensitivity including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for these reactions.
There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.

DRUG INTERACTIONS

Periodically monitor digoxin plasma levels due to increased $C_{\text{max}}$ and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as ESAs or estrogen-containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

USE IN SPECIFIC POPULATIONS

- **PREGNANCY: See Boxed WARNINGS:** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

- **LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.

- **RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis.


Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, for REVLIMID on the following pages.
REVLIMID [lenalidomide], Capsules for oral use

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment [see Warnings and Precautions (5.1), and Medication Guide (17)]. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program (5.2).

Information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors [see Dosage and Administration (2.2)].

Venous and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient’s underlying risks [see Warnings and Precautions (5.4)].

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

REVLIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT).

1.6 Limitations of Use

REVLIMID is not indicated and is not recommended for the treatment of patients with CLL outside of controlled clinical trials [see Warnings and Precautions (5.5)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Multiple Myeloma

For patients who are auto-HSCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a REVLIMID-containing therapy [see Warnings and Precautions (5.12)].

REVLIMID Maintenance Therapy Following Auto-HSCT

Following auto-HSCT, initiate REVLIMID maintenance therapy after adequate hematologic recovery (ANC at least 1000/mcL and/or platelet counts at least 75,000/mcL). The recommended starting dose of REVLIMID is 10 mg once daily continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.

Dose Adjustments for Hematologic Toxicities During MM Treatment

Dose modification guidelines, as summarized in Table 2 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.

2.2 Recommended Dosage for Patients with Renal Impairment

Table 3: Dose Adjustments for Patients with Renal Impairment

Renal Function (Cockcroft-Gault) Dose in REVLIMID Maintenance Therapy Following Auto-HSCT for MM

<table>
<thead>
<tr>
<th>Clcr 30 to 60 mL/min</th>
<th>5 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clcr below 30 mL/min (not requiring dialysis)</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>Clcr below 30 mL/min (requiring dialysis)</td>
<td>2.5 mg once daily On dialysis days, administer the dose following dialysis.</td>
</tr>
</tbody>
</table>

REVLIMID Maintenance Therapy Following Auto-HSCT for MM: Base subsequent REVLIMID dose increase or decrease on individual patient treatment tolerance [see Dosage and Administration (2.1)].

2.7 Administration

Advise patients to take REVLIMID orally at about the same time each day, either with or without food. Advise patients to swallow REVLIMID capsules whole with water and not to open, break, or chew them.

4 CONTRAINDICATIONS

4.1 Pregnancy

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide’s structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant [see Boxed Warning]. 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 risk to a fetus [see Warnings and Precautions (5.1, 5.2). Use in Special Populations (8.1, 8.3)].
REVLIMID® [lenalidomide], Capsules for oral use

4.2 Severe Hypersensitivity Reactions

REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [see Warnings and Precautions (5.9, 5.15)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes birth defects and/or embryonic death [see Use in Specific Populations (8.1)]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS program [see Warnings and Precautions (5.2)].

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and for 4 weeks following discontinuation of REVLIMID therapy. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles [see Use in Specific Populations (8.3)].

Males

Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm [see Use in Specific Populations (8.3)].

Blood Donation

Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 REVLIMID REMS Program

Because of the embryo-fetal risk [see Warnings and Precautions (5.1)], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the REVLIMID REMS program.

Required components of the REVLIMID REMS program include the following:

- Prescribers must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.3)] and males must comply with contraception requirements [see Use in Specific Populations (8.3)].
- Pharmacies must be certified with the REVLIMID REMS program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the REVLIMID REMS program is available at www.valeantpharmaceuticalsmanagement.com or by telephone at 1-888-423-5436.

5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking REVLIMID should have their complete blood counts assessed periodically as described below [see Dosage and Administration (2.1, 2.2, 2.3)].

Monitor complete blood counts (CBC) in patients taking REVLIMID in combination with dexamethasone or as REVLIMID maintenance therapy for MM every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter. A dose interruption and/or dose reduction may be required [see Dosage and Administration (2.1)]. In the MM maintenance therapy arm, Grade 3 or 4 thrombocytopenia was reported in up to 59% of REVLIMID-treated patients and Grade 3 or 4 thrombocytopenia in up to 38% of REVLIMID-treated patients [see Adverse Reactions (6.1)].

5.4 Venous and Arterial Thromboembolism

Venous thromboembolic events (VTE [DVT and PE]) and arterial thromboembolic events (ATE, myocardial infarction and stroke) are increased in patients treated with REVLIMID.

A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with MM after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (1.3% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively) [see Boxed Warning and Adverse Reactions (6.1)]. Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with MM after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6%, and 0.6%, respectively) [see Adverse Reactions (6.1)].

Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed MM who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone. The median time to first thrombosis event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.3 months in the combined Rd Continuous and Rd16 Arms.

In the AUGMENT trial, the incidence of VTE (including DVT and PE) in FL or MZL patients was 3.4% in the REVLIMID/rituximab arm [see Adverse Reactions (6.1)]. In the AUGMENT trial, the incidence of ATE (including MI) in FL or MZL patients was 0.6% in the REVLIMID/rituximab arm [see Adverse Reactions (6.1)].

Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID [see Drug Interactions (7.2)].

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies

In clinical trials in patients with MM receiving REVLIMID, an increase in hematologic plus solid tumor second primary malignancies (SPM) notably AML and MDS have been observed. An increase in hematologic SPM including AML and MDS occurred in 5.3% of patients with NDMM receiving REVLIMID in combination with oral melphalan compared with 1.3% of patients receiving melphalan without REVLIMID. The frequency of AML and MDS cases in patients with NDMM treated with REVLIMID in combination with dexamethasone without melphalan was 0.4%.

In patients receiving REVLIMID maintenance therapy following high dose intravenous melphalan and auto-HSCT, hematologic SPM occurred in
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7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma, and basal cell carcinoma, occurred in 3.9% of patients receiving REVLIMID maintenance, compared to 2.6% in the placebo arm.

In patients with relapsed or refractory MM treated with REVLIMID/dexamethasone, the incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 2.3% versus 0.6% in the dexamethasone alone arm. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.1% of patients receiving REVLIMID/dexamethasone, compared to 0.6% in the dexamethasone alone arm.

Patients who received REVLIMID-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated with REVLIMID maintenance. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

In the AUGMENT trial with FL or MZL patients receiving REVLIMID/rituximab therapy, hematologic plus solid tumor SPMs, notably AML, have been observed. In the AUGMENT trial, hematologic SPM of AML occurred in 0.8% of patients with FL or MZL receiving REVLIMID/rituximab therapy. The incidence of hematologic plus solid tumor SPMs (excluding non-melanoma skin cancers) was 1.7% in the REVLIMID/rituximab arm with a median follow-up of 29.8 months (range 0.5 to 51.3 months) [see Adverse Reactions (6.1)]. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

5.7 Increased Mortality in Patients with MM When Pemritozumab Is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with MM, the addition of pomalidomide to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

5.8 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestasis and mixed characteristics); 2% of patients with MM and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.9 Severe Cutaneous Reactions

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) may be reported. DRSS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS [see Dosage and Administration (2.5)].

5.10 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Monitor patients at risk closely and take appropriate preventive approaches. In the AUGMENT trial in FL or MZL patients, TLS occurred in 2 patients (1.1%) in the REVLIMID/rituximab arm. TLS occurred in 1 patient (0.5%) in the MAGNIFY trial during the REVLIMID/rituximab induction period; the event was a serious, Grade 3 adverse reaction.

5.11 Tumor Flare Reaction

Tumor flare reaction (TFR) has occurred during investigational use of REVLIMID for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. Tumor flare reaction may mimic progression of disease (PD).

In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in Cycle 1 and one patient developed TFR again in Cycle 11. In the AUGMENT trial in FL or MZL patients, TFR was reported in 18/176 (10.3%) of patients in the REVLIMID with rituximab arm; one patient in the REVLIMID/rituximab arm experienced a Grade 3 TFR. In the MAGNIFY trial, 9/222 (4.1%) of patients experienced TFR; all reports were Grade 1 or 2 in severity and 1 event was considered as serious.

REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

5.12 Impaired Stem Cell Mobilization

A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are auto-HSCT candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a REVLIMID-containing treatment or for whom inadequate numbers of CD34+ cells have been collected with G-CSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

5.13 Thyroid Disorders

Both hypothyroidism and hyperthyroidism have been reported [see Adverse Reactions (6.2)]. Measure thyroid function before start of REVLIMID treatment and during therapy.

5.14 Early Mortality in Patients with MCL

In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the REVLIMID arm versus 7.1% in the control arm. On exploratory multivariate analysis, risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥ 10 x 10^9/L).

5.15 Hypersensitivity

Hypersensitivity, including angioedema, anaphylaxis, and anaphylactoid reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for angioedema and anaphylaxis [see Dosage and Administration (2.2)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in other sections of the prescribing information:

- Embryo-Fetal Toxicity [see Boxed Warning, Warnings and Precautions (5.1, 5.2)]
- Hematologic Toxicity [see Boxed Warning, Warnings and Precautions (5.3)]
- Venous and Arterial Thromboembolism [see Boxed Warning, Warnings and Precautions (5.4)]
- Increased Mortality in Patients with CLL [see Warnings and Precautions (5.5)]
- Second Primary Malignancies [see Warnings and Precautions (5.6)]
- Increased Mortality in Patients with MM When Pemritozumab Is Added to a Thalidomide Analogue and Dexamethasone [see Warnings and Precautions (5.7)]
- Hepatotoxicity [see Warnings and Precautions (5.8)]
- Severe Cutaneous Reactions Including Hypersensitivity Reactions [see Warnings and Precautions (5.9)]
- Tumor Lysis Syndrome [see Warnings and Precautions (5.10)]
- Tumor Flare Reactions [see Warnings and Precautions (5.11)]
- Impaired Stem Cell Mobilization [see Warnings and Precautions (5.12)]
- Thyroid Disorders [see Warnings and Precautions (5.13)]
- Early Mortality in Patients with MCL [see Warnings and Precautions (5.14)]
- Hypersensitivity [see Warnings and Precautions (5.15)]

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.

Newly Diagnosed MM - REVLIMID Maintenance Therapy Following Auto-HSCT

Data were evaluated from 1018 patients in two randomized trials who received at least one dose of REVLIMID 10 mg daily as maintenance therapy after auto-HSCT until progressive disease or unacceptable toxicity. The mean treatment duration for REVLIMID treatment was 30.3 months for Maintenance Study 1 and 24.0 months for Maintenance Study 2 (overall range across both studies from 0.1 to 108 months). As of the cut-off date of 1 Mar 2015, 48 patients (21%) in the Maintenance
REVLIMID [lenalidomide], Capsules for oral use

For REVLIMID, the most common adverse reactions leading to dose interruption were hematologic events (29.7%, data available in Maintenance Study 2 only). The most common adverse reaction leading to dose reduction of REVLIMID were hematologic events (17.7%, data available in Maintenance Study 2 only). The most common adverse reactions leading to discontinuation of REVLIMID were thrombocytopenia (2.7%) in Maintenance Study 1 and neutropenia (2.4%) in Maintenance Study 2. The frequencies of onset of adverse reactions were generally highest in the first 6 months of treatment and then the frequencies decreased over time or remained stable throughout treatment.

Table 5 summarizes the adverse reactions reported for the REVLIMID and placebo maintenance treatment arms.

### Table 5: All Adverse Reactions in ≥5% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM in the REVLIMID Vs Placebo Arms

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>Maintenance Study 1</th>
<th>Maintenance Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REVLIMID (N=224) n (%)</td>
<td>Placebo (N=221) n (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia ≥5%</td>
<td>177 (79)</td>
<td>94 (43)</td>
</tr>
<tr>
<td>Thrombocytopenia ≥5%</td>
<td>162 (72)</td>
<td>101 (46)</td>
</tr>
<tr>
<td>Leukopenia ≥5%</td>
<td>51 (23)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47 (21)</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>40 (18)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>Pancytopenia c,d ≥5%</td>
<td>&lt;1%</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Febrile neutropenia c,d</td>
<td>39 (17)</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection c</td>
<td>60 (27)</td>
<td>35 (16)</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>40 (18)</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Pneumonia c,d</td>
<td>31 (14)</td>
<td>15 (7)</td>
</tr>
<tr>
<td>Bronchitis c</td>
<td>10 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Nasopharyngitis c</td>
<td>5 (2)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gastroenteritis c</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rhinitis c</td>
<td>&lt;1%</td>
<td>0 (0)</td>
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<tr>
<td>Sinusitis c</td>
<td>8 (4)</td>
<td>3 (1)</td>
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<td>Influenza c</td>
<td>8 (4)</td>
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<td>Lung infection c</td>
<td>21 (9)</td>
<td>&lt;1%</td>
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<tr>
<td>Lower respiratory tract infection c</td>
<td>13 (6)</td>
<td>5 (2)</td>
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<tr>
<td>Infection c</td>
<td>12 (5)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Urinary tract infection c,d</td>
<td>9 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Lower respiratory tract infection bacterial d</td>
<td>6 (3)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Bacteremia d</td>
<td>5 (2)</td>
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<tr>
<td>Herpes zoster c,d</td>
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<td>10 (5)</td>
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<tr>
<td>Sepsis c,d</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
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<td>Gastrointestinal disorders</td>
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<tr>
<td>Diarrhea</td>
<td>122 (54)</td>
<td>83 (38)</td>
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<tr>
<td>Nausea</td>
<td>33 (15)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (8)</td>
<td>12 (5)</td>
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<tr>
<td>Constipation               c,d</td>
<td>12 (5)</td>
<td>8 (4)</td>
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<tr>
<td>Abdominal pain c,d</td>
<td>8 (4)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Abdominal pain upper c,d</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

(continued)
### REVLIMID [lenalidomide], Capsules for oral use

#### Table 5: All Adverse Reactions in ≥5% and Grade 3/4 Adverse Reactions in ≥1% of Patients with MM in the REVLIMID Vs Placebo Arms*  

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Maintenance Study 1</th>
<th></th>
<th>Maintenance Study 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Adverse Reactions a</td>
<td>Grade 3/4 Adverse Reactions b</td>
<td>All Adverse Reactions a</td>
<td>Grade 3/4 Adverse Reactions b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>REVLIMID (N=224) n (%)</td>
<td>Placebo (N=221) n (%)</td>
<td>REVLIMID (N=224) n (%)</td>
<td>Placebo (N=221) n (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td>0 ( 0)</td>
<td>&lt; 1%</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>51 (23)</td>
<td>30 ( 14)</td>
<td>21 ( 9)</td>
<td>9 ( 4)</td>
</tr>
<tr>
<td>Pyrexia e</td>
<td></td>
<td>17 ( 8)</td>
<td>10 ( 5)</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin *</td>
<td></td>
<td>9 ( 4)</td>
<td>4 ( 2)</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>71 (32)</td>
<td>48 (22)</td>
<td>11 ( 5)</td>
<td>5 ( 2)</td>
</tr>
<tr>
<td>Priapism</td>
<td></td>
<td>9 ( 4)</td>
<td>4 ( 2)</td>
<td>3 ( 1)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia *</td>
<td></td>
<td>&lt; 1%</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Peripheral neuropathy * e</td>
<td></td>
<td>34 (15)</td>
<td>30 (14)</td>
<td>8 ( 4)</td>
<td>8 ( 4)</td>
</tr>
<tr>
<td>Headache d</td>
<td></td>
<td>11 ( 5)</td>
<td>8 ( 4)</td>
<td>5 ( 2)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td></td>
<td>16 ( 7)</td>
<td>3 ( 1)</td>
<td>8 ( 4)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td></td>
<td>13 ( 6)</td>
<td>5 ( 2)</td>
<td>6 ( 3)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>increased d</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td>24 (11)</td>
<td>13 ( 6)</td>
<td>16 ( 7)</td>
<td>12 ( 5)</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
<td>9 ( 4)</td>
<td>5 ( 2)</td>
<td>7 ( 3)</td>
<td>3 ( 1)</td>
</tr>
<tr>
<td>Hypophosphatemia e</td>
<td></td>
<td>16 ( 7)</td>
<td>15 ( 7)</td>
<td>13 ( 6)</td>
<td>14 ( 6)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms e</td>
<td></td>
<td>0 ( 0)</td>
<td>&lt; 1%</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Myalgia e</td>
<td></td>
<td>7 ( 3)</td>
<td>8 ( 4)</td>
<td>3 ( 1)</td>
<td>5 ( 2)</td>
</tr>
<tr>
<td>Musculoskeletal pain e</td>
<td></td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia e</td>
<td></td>
<td>34 (15)</td>
<td>19 ( 9)</td>
<td>4 ( 2)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough e</td>
<td></td>
<td>23 (10)</td>
<td>12 ( 5)</td>
<td>3 ( 1)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Dyspnea e</td>
<td></td>
<td>15 ( 7)</td>
<td>9 ( 4)</td>
<td>8 ( 4)</td>
<td>4 ( 2)</td>
</tr>
<tr>
<td>Rhinorrhea e</td>
<td></td>
<td>0 ( 0)</td>
<td>3 ( 1)</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Pulmonary embolism c d e</td>
<td></td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
<td>0 ( 0)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis e f</td>
<td></td>
<td>8 ( 4)</td>
<td>&lt; 1%</td>
<td>5 ( 2)</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome e f</td>
<td></td>
<td>5 ( 2)</td>
<td>0 ( 0)</td>
<td>&lt; 1%</td>
<td>0 ( 0)</td>
</tr>
</tbody>
</table>

**Note:** Adverse Events (AEs) are coded to Body System/Adverse Reaction using MedDRA v15.1. A subject with multiple occurrences of an adverse reaction is counted only once under the applicable Body System/Adverse Reaction.

- All treatment-emergent AEs in at least 5% of patients in the REVLIMID Maintenance group and at least 2% higher frequency (%) than the Placebo Maintenance group.
- All grade 3 or 4 treatment-emergent AEs in at least 1% of patients in the REVLIMID Maintenance group and at least 1% higher frequency (%) than the Placebo Maintenance group.
- All serious treatment-emergent AEs in at least 1% of patients in the REVLIMID Maintenance group and at least 2% higher frequency (%) than the Placebo Maintenance group.
- Footnote “a” not applicable for either study
- Footnote “b” not applicable for either study
- Footnote “c” ADRs where at least one resulted in a fatal outcome
- Footnote “d” ADRs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
- Footnote “e” Adverse Reactions for combined ADR terms (based on relevant TEAE PTs included in Maintenance Studies 1 and 2 [per MedDRA v 15.1]).

**Abbreviations:** Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis
REVLIMID [lenalidomide], Capsules for oral use

Deep vein thrombosis
Peripheral sensory neuropathy, Polyneuropathy
Staphylococcal sepsis

6.2 Postmarketing Experience
The following adverse drug reactions have been identified from the worldwide post-marketing experience with REVLIMID. 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 [see Warnings and Precautions Section (5.8 to 5.11, and 5.13)].

Endocrine disorders: Hypothyroidism, hyperthyroidism
Hepatic disorders: Hepatitis, cholestatic hepatitis, cholestasis
Infections and infestations: Herpes zoster, varicella
Lymphatic System Disorders: Lymphopenia
Neoplasms benign, malignant and unspecified (including cysts and polyps): Malignant neoplasms of the skin
Neurological disorders: Abnormal States and Conditions, including behavior disorders, disturbance of consciousness, encephalopathy, facial nerve palsy, Guillain-Barré syndrome, headache, increased intracranial pressure, intracranial hypertension, myelopathy, peripheral neuropathy, polyneuropathy, sleep disorders
Psychiatric disorders: Affective disorder, anxiety, anger, apathy, anxiety and agitation, anxiety and depression, anxiety and irritability, anger and anxiety, anger and irritability, anxiety, anxiety and depression, behavior disturbances, fear, hostility, hostility and anxiety, hostility and irritability, irritability, irritability and anxiety, irritability and depression, irritability and hostility, irritability and sleep disturbance, irritability and suicidal ideation, irritability and suicidal ideation and aggression, melatonin rebound insomnia, mental depression, mental depression and anxiety, mental depression and irritability, mental depression and suicidal ideation, mental depression and suicidal ideation and aggression, mental depression and suicide, mental depression and suicidal ideation, mental depression and suicide and aggression, mental depression and suicide and aggression
Psychological and Behavioral Disorders: Behavioral abnormalities
Sensory System Disorders: Blurred vision, conjunctivitis, retinopathy, optic atrophy
Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome
Vascular disorders: Thrombosis

7 Drug Interactions

7.1 Digoxin
When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin Cmax and AUC were increased by 14%. Periodically monitor digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, during administration of REVLIMID.

7.2 Concomitant Therapies That May Increase the Risk of Thrombosis
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [see Warnings and Precautions (5.4)].

7.3 Warfarin
Co-administration of multiple doses of REVLIMID (10 mg/day) with a single dose of warfarin (25 mg) had no effect on the pharmacokinetics of lenalidomide or P- and K-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Risk Summary
Based on the mechanism of action [see Clinical Pharmacology (12.1)] and findings from animal studies [see Data], REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see Boxed Warning. Contraindications (4.1), and Use in Specific Populations (5.1)].

REVLIMID is a thalidomide analogue. Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasia of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. Lenalidomide crossed the placenta after administration to pregnant rabbits and pregnant rats [see Data]. 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 risk to a fetus. If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

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

Data

Animal data
In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest fetal dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide. Following daily oral administration of lenalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma lenalidomide concentrations were approximately 20%-40% of the maternal Cmax. Following a single oral dose to pregnant rats, lenalidomide was detected in fetal plasma and tissues; concentrations of radioactivity in fetal tissues were generally lower than those in maternal tissues. These data indicated that lenalidomide crossed the placenta.

8.2 Lactation

Risk Summary
There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed child, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children from REVLIMID, advise women not to breastfeed during treatment with REVLIMID.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing
REVLIMID can cause fetal harm when administered during pregnancy [see Use in Specific Populations (8.1)]. Verify the pregnancy status of females of reproductive potential prior to initiating REVLIMID therapy and during therapy. Advise females of reproductive potential that they must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.
**REVLIMID** [lenalidomide], Capsules for oral use

**Contraception**

**Females**

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner’s vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

**Males**

Lenalidomide is present in the semen of males who take REVLIMID. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm.

**8.4 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

**8.5 Geriatric Use**

MM Maintenance Therapy: Overall, 10% (106/1018) of patients were 65 years of age or older, while no patients were over 75 years of age. Grade 3 or 4 adverse reactions were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. The frequency of Grade 3 or 4 adverse reactions in the Blood and Lymphatic System Disorders were higher in the REVLIMID arm (more than 5% higher) in the patients 65 years of age or older versus younger patients. There were not a sufficient number of patients 65 years of age or older in REVLIMID maintenance studies who experienced either a serious adverse reaction, or discontinued therapy due to an adverse reaction to determine whether elderly patients respond relative to safety differently from younger patients. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

**8.6 Renal Impairment**

Adjust the starting dose of REVLIMID based on the creatinine clearance value and for patients on dialysis [see Doseage and Administration (2.6)].

**10 OVERDOSAGE**

There is no specific experience in the management of REVLIMID overdose in patients with MM, MDS, MCL, FL, or MZL. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with lenalidomide have not been conducted. Lenalidomide was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, or mutations at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times the human dose of 25 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

**17 PATIENT COUNSELING INFORMATION**

Advertise the patient to read the FDA-approved Patient labeling (Medication Guide)

**Embryo-Fetal Toxicity**

Advertise patients that REVLIMID is contraindicated in pregnancy [see Boxed Warning and Contraindications (4.1)]. REVLIMID is a thalidomide analogue and can cause serious birth defects or death to a developing baby [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].

- Advise females of reproductive potential that they must avoid pregnancy while taking REVLIMID and for at least 4 weeks after completing therapy.
- Initiate REVLIMID treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use 2 different forms of contraception including at least 1 highly effective form, simultaneously during REVLIMID therapy, during dose interruption and for 4 weeks after she has completely finished taking REVLIMID. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch or implants) and a partner’s vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm and cervical cap.
- Instruct patient to immediately stop taking REVLIMID and contact her healthcare provider if she becomes pregnant while taking this drug, if she misses her menstrual period, or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her healthcare provider is not available, she should call Celgene Customer Care Center at 1-888-423-5436 [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy.
- Advise male patients taking REVLIMID that they must not donate sperm [see Warnings and Precautions (5.1) and Use in Specific Populations (8.3)].
- All patients must be instructed to not donate blood while taking REVLIMID, during dose interruptions and for 4 weeks following discontinuation of REVLIMID [see Warnings and Precautions (5.1)].

**REVLIMID REMS program**

Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID REMS program [see Warnings and Precautions (5.2)].

- Patients must sign a Patient-Physician agreement form and comply with the requirements to receive REVLIMID. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements and participate in monthly telephone surveys. Males must comply with the contraception requirements [see Use in Specific Populations (8.3)].
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

**Pregnancy Exposure Registry**

Inform females there is a Pregnancy Exposure Registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy and that they can contact the Pregnancy Exposure Registry by calling 1-888-423-5436 [see Use in Specific Populations (8.1)].

**Hematologic Toxicity**

Inform patients that REVLIMID is associated with significant neutropenia and thrombocytopenia [see Boxed Warning and Warnings and Precautions (5.3)].

**Venous and Arterial Thromboembolism**

Inform patients of the risk of thrombosis including DVT, PE, MI, and stroke and to report immediately any signs and symptoms suggestive of these events for evaluation [see Boxed Warning and Warnings and Precautions (5.4)].

**Increased Mortality in Patients with CLL**

Inform patients that REVLIMID had increased mortality in patients with CLL and serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure [see Warnings and Precautions (5.5)].

**Second Primary Malignancies**

Inform patients of the potential risk of developing second primary malignancies during treatment with REVLIMID [see Warnings and Precautions (5.6)].
**Hepatotoxicity**
Inform patients of the risk of hepatotoxicity, including hepatic failure and death, and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.8)].

**Severe Cutaneous Reactions**
Inform patients of the potential risk for severe skin reactions such as SJS, TEN, and DRESS and report any signs and symptoms associated with these reactions to their healthcare provider for evaluation. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID [see Warnings and Precautions (5.9)].

**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 (5.10)].

**Tumor Flare Reaction**
Inform patients of the potential risk of tumor flare reaction and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see Warnings and Precautions (5.11)].

**Early Mortality in Patients with MCL**
Inform patients with MCL of the potential for early death [see Warnings and Precautions (5.14)].

**Hypersensitivity**
Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to REVLIMID. Instruct patients to contact their healthcare provider right away for signs and symptoms of these reactions. Advise patients to seek emergency medical attention for signs or symptoms of severe hypersensitivity reactions [see Warnings and Precautions (5.15)].

**Dosing Instructions**
Inform patients how to take REVLIMID [see Dosage and Administration (2)]:
- REVLIMID should be taken once daily at about the same time each day.
- REVLIMID may be taken either with or without food.
- The capsules should not be opened, broken, or chewed. REVLIMID should be swallowed whole with water.
- Instruct patients that if they miss a dose of REVLIMID, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take REVLIMID at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

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Panobinostat Triplet Elicits Responses in Relapsed Myeloma

by GINA MAURO

COMBINING A HIGHER DOsing

schedule of panobinostat (Farydak) with subcutaneous bortezomib (Velcade) and dexamethasone (FVd) led to durable responses and an acceptable safety profile in patients with relapsed or relapsed/refractory myeloma, according to results of the phase 2 PANORAMA 3 trial (NCT02654990) presented during ASH 2020.1

After up to 8 treatment cycles, findings showed that the objective response rates (ORRs) were 62.2%, 65.1%, and 50.6% in patients who received the triplet with a panobinostat dose of 20 mg 3 times weekly dose, 20 mg twice weekly dose, and 10 mg 3 times-weekly dose of panobinostat, respectively. The median time to response was 1 month, 2 months, and 3 months, respectively; the median duration of response (DOR) was 22 months (14—not estimable), 12 months, and 11 months, respectively.

Additionally, the rates of adverse events (AEs) at the highest panobinostat dose were lower than what had been observed at the same dose level in the PANORAMA-1 trial (NCT01023308) with intravenous (IV) bortezomib, suggesting that the subcutaneous administration of the proteasome inhibitor improves tolerability, explained lead study author Jacob Laubach, MD, MPP. However, the 10-mg 3-times-weekly regimen was the best tolerated of the 3 dosing schedules.

“This study supports the use of this 3-drug regimen with subcutaneous bortezomib in combination with panobinostat,” said Laubach, who is clinical director of the Jerome Lipper Multiple Myeloma Center and senior physician at Dana-Farber Cancer Institute, as well as assistant professor of medicine at Harvard Medical School, in Boston, Massachusetts. “The study supports the fact that panobinostat, bortezomib, and dexamethasone is an important treatment option for patients who have become refractory to standard agents, including [immunomodulatory drugs], proteasome inhibitors, and CD38 monoclonal antibodies, with the appropriate dose and schedule modifications to minimize toxicity.” Laubach shared the findings in a virtual poster presentation during the meeting.

Previously, PANORAMA-1 results showed a significant benefit in progression-free survival (PFS) with FVd compared with placebo and bortezomib/dexamethasone. However, AEs were more frequent with the panobinostat regimen compared with bortezomib/dexamethasone (grade 3/4, 96% vs 82%).2

PANORAMA 3, an open-label, international, multicenter, phase 2 trial, randomized patients to receive 1 of 3 dosing schedules of panobinostat and incorporated subcutaneous bortezomib/dexamethasone. For cycles 1 through 4, all patients younger than 75 years received subcutaneous bortezomib at 1.3 mg/m² twice weekly and oral dexamethasone at 20 mg 4 times per week.

Those younger than 75 years from cycle 5 onward, and all patients older than 75 years, received bortezomib subcutaneously at 1.3 mg/m² weekly and oral dexamethasone at 20 mg twice a week; patients older than 75 years were given dexamethasone at a 10-mg twice-weekly dose.1

Treatment was administered until disease progression, death, discontinuation due to toxicity, or consent withdrawal.

To be eligible for enrollment, patients must have been at least 18 years old, had relapsed or relapsed/refractory myeloma per International Myeloma Working Group 2014 criteria, and previously received 1 to 4 prior lines of treatment, including an immunomodulatory agent. Patients who were refractory to bortezomib could not enroll.

In the 20-mg 3-times-weekly dose (n = 82), the stringent complete response (sCR) rate was 1.2%, the complete response (CR) rate was 3.7%, the very good partial response (VGPR) rate was 24.4%, the partial response (PR) rate was 32.9%, and the minimal response rate was 8.5%. A total 18.3% of patients had stable disease (SD), 1 patient (1.2%) experienced disease progression (PD), and 9.8% of patients had unknown responses.

For the 20-mg twice-weekly dose (n = 83), the sCR, CR, VGPR, and PR rates were 0%, 3.6%, 28.9%, and 32.5%, respectively, and 12% of patients achieved a minimal response. The SD rate was 15.7%, and 1 patient experienced PD. Five patients (6.0%) had unknown responses.

Finally, in the 10-mg 3-times-weekly dose (n = 83), the sCR rate was 4.8%, the CR rate was 1.2%, the VGPR rate was 19.3%, the PR rate was 25.3%, and the minimal response rate was 9.6%. SD was the best response in 30.1% of patients, and 3.6% of patients had PD. Five patients (6.0%) had unknown responses.

At 1 year, the PFS probability was 53% in the 20-mg 3-times-weekly dose, 51% in the 20-mg twice-weekly dose, and 33% in the 10-mg 3-times-weekly dose.

Regarding safety, AEs were more common in the two 20-mg dosing schedules of panobinostat. Grade 3 or higher AEs occurred in 91.0%, 83.1%, and 75.0% of patients receiving 20 mg 3 times weekly, 20 mg twice weekly, and 10 mg 3 times weekly, respectively. AEs that led to discontinuation were 29.5%, 27.7%, and 15.0%, respectively.

Treatment-related AEs (TRAEs) occurred at 94.9% with the 20-mg 3-times-weekly dose, 96.4% with the 20-mg twice-weekly dose, and 91.3% with the 10-mg 3-times-weekly dose. Serious AEs occurred in 53.8%, 48.2%, and 43.8% of patients, respectively.

On-treatment deaths were highest in the 10-mg 3-times-weekly arm (n = 6) compared with 5 in the 20-mg 3-times-weekly arm and 3 in the 20-mg twice weekly arm. No deaths were causally related to treatment.

AEs of special interest included all-grade and grade 3 or higher severe hemorrhage and thrombocytopenia, seen with the dose of 20 mg 3 times-weekly (all-grade, 65.4%; grade 3, 52.6%), 20 mg twice weekly (55.4% and 37.3%, respectively), and 10 mg 3 times weekly (38.8% and 28.8%). Additionally, all-grade and grade 3 or higher severe diarrhea was similar across all 3 doses.
Momelotinib Trial Seeks to Address Myelofibrosis Symptoms

by DENISE MYSHKO

Momelotinib, an orally administered novel agent, is being evaluated in a phase 3 trial in patients with symptomatic and anemic myelofibrosis (MF), a population that experts say is in need of new options. The MOMENTUM trial (NCT04173494) will randomize patients who have previously received a JAK inhibitor to receive momelotinib or danazol to determine which regimen shows more efficacy against the MF hallmarks of anemia, constitutional symptoms, and splenomegaly.1

Momelotinib is a small-molecule inhibitor of the Janus kinases 1 and 2 (JAK1/2) and activin A receptor type-I (ACVR1).1 Danazol, a synthetic steroid that the FDA has approved for patients with endometriosis and hereditary angioedema, is included in National Comprehensive Cancer Network guidelines as a treatment for anemia in patients with MF, resulting in reduction of iron availability and symptoms. They really have made an important impact on the disease, but they don't help with anemia.”

Momelotinib’s anemia benefit is primarily achieved through direct inhibition of the kinase ACVR1, a member of the transforming growth factor β receptor family that influences production of hepcidin, an iron regulatory hormone. Hepcidin is often elevated in patients with MF, resulting in reduction of iron availability and restriction of erythropoiesis.4 “It’s thought that an additional contributor to the anemia in myelofibrosis is hepcidin and that an inflammatory environment might be suppressing hematopoiesis. By alleviating that, there can be an improvement in erythropoiesis and a decrease in anemia,” Mesa said.

**MOMENTUM FOCUSES ON SYMPTOMS**

In the MOMENTUM trial, patients are being randomized 2:1 to momelotinib plus placebo or danazol plus placebo. At the end of week 24, patients randomized to momelotinib can continue on treatment up to approximately 4 years. Patients who received danazol may cross over to momelotinib or continue to receive danazol (FIGURE).

Mesa said the choice of a comparative therapy for the study was challenging. “Danazol is one of the most widely available agents that has some activity for anemia. It is a relatively well-tolerated drug with response rates of 20% to 30%. We think this was the strongest control arm that could be offered. It highlights why there is such significant unmet need for these patients.”

The primary end point will be Total Symptom Score (TSS) response rate using the Myelofibrosis Symptom Assessment Form version 4.0, with the response rate defined as the proportion of patients who achieve a reduction of 50% or more over the 28 days before the end of week 24 of therapy. Key secondary end points will include transfusion independence (TI) and splenic response rate (SRR) at 24 weeks. TI is defined as not requiring red blood cell (RBC) transfusion for 12 weeks or longer and splenic response

**FIGURE.** Momelotinib Evaluated in Myelofibrosis

**Phase 3 MOMENTUM Trial**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Primary end point</th>
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<tr>
<td>Double-blind treatment</td>
<td>Week 24</td>
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<tr>
<td>Open label/cross over</td>
<td>Long-term follow-up</td>
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**Key eligibility criteria**

- Confirmed diagnosis of primary MF or post-PV/ET MF
- Previously treated with a JAK inhibitor
- Symptomatic (TSS ≥ 10)
- Anemia (Hgb < 10 g/dL)
- Splenomegaly (palpable spleen at ≥ 5 cm)

<table>
<thead>
<tr>
<th>2:1 randomization</th>
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<td>N = 180</td>
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<table>
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<tr>
<th>Momelotinib 200 mg daily + placebo</th>
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<tr>
<td><em>Spleen progression (momelotinib 200 mg)</em></td>
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<tr>
<th>Danazol 600 mg daily + placebo</th>
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<td>Mamolotinib 200 mg daily</td>
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**Primary: TSS at week 24 (≥50% reduction)*

**Secondary:**

- Transfusion independence (≥ 12 weeks)
- Splenic response rate at week 24

ET, post-essential thrombocythemia; Hgb, hemoglobin; MF, myelofibrosis; PV, post-polycythemia vera; TSS, Total Symptom Score.

*Early crossover to open label in the event of confirmed symptomatic splenic progression.

*Assessed on the Myelofibrosis Symptom Assessment Form version 4.0.
is defined as a reduction in spleen volume of 35% or more from baseline with hemoglobin level ≥ 8 g/dL.

“This trial puts symptoms of myelofibrosis front and center as one of the primary end points,” Mesa said. “We’re trying to make an impact on the patient’s overall quality of life, and we are hopeful about this trial in terms of the overt symptoms that patients face. I envision it will impact their quality of life both in terms of symptoms but also in terms of the burden of being transfusion dependent. We recognized that being transfusion dependent is a tremendous burden on our patients.”

Investigators aim to recruit 180 patients through more than 150 sites in the United States and other countries. Sierra Oncology, which is developing the therapy, expects enrollment to be completed by the middle of 2021 and top-line data to be reported in the first half of 2022.5

EARLY FINDINGS VARY
Clinical development of momelotinib in MF has been under way for more than 7 years, and more than 800 patients with the malignancy have received the drug in several settings.6 Sierra Oncology has provided access to momelotinib for patients with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF who participated in prior studies.7 Of the 137 patients who have enrolled in the extended-access protocol, 105 remain on momelotinib therapy including some who have taken the drug for up to 10 years.6

In the phase 3 SIMPLIFY-1 trial (NCT01969838), momelotinib was compared with ruxolitinib in 432 patients who had not received prior JAK inhibitor therapy and who had MF classified as high- or intermediate-2 risk or symptomatic intermediate-1 risk on the International Prognostic Scoring System.8

Primary findings showed that momelotinib met the statistical threshold for noninferiority to ruxolitinib for spleen response (P = .011) but not for TSS (P = .98). Nevertheless, patients who received momelotinib had a higher rate of TI at 24 weeks than those who took ruxolitinib (65.5% vs 49.3%, respectively), a lower rate of transfusion dependence (30.2% vs 40.1%), and a lower median RBC requirement (0.0 vs 0.4 units/month).8

The phase 3 SIMPLIFY-2 trial (NCT02101268) was conducted in 156 patients with MF who had suboptimal responses or hematological toxicity during prior ruxolitinib therapy. Participants were randomized 2:1 to momelotinib at 200 mg daily or best available therapy, which could include ruxolitinib, chemotherapy, steroids, no treatment, or other standard intervention. Most patients (89%) received ruxolitinib.9

Findings showed reduction in spleen volume of 35% or more in 7% of patients who received momelotinib versus 6% in the ruxolitinib/best available therapy group, for a proportion difference of 0.01 (95% CI, 0.09-0.10; P = .90).9

LONG-TERM UPDATES ENHANCE PROFILE
Overall, findings from the SIMPLIFY studies show that momelotinib provides splenic responses similar to ruxolitinib while improving constitutional symptoms, reducing the RBC burden, and improving anemia, Srdan Verstovsek, MD, PhD, said during a presentation at the 62nd American Society of Hematology Annual Meeting and Exposition in December (ASH 2020).9

“Momelotinib is the only JAK inhibitor [that] may be able to provide benefit for each of the 3 main features of myelofibrosis,” said Verstovsek, who is director of the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms at The University of Texas MD Anderson Cancer Center in Houston. “Importantly, momelotinib accomplishes this while demonstrating a favorable safety profile, which includes relatively low rates of grade 3 thrombocytopenia and anemia.”

Verstovsek and colleagues retrospectively examined long-term outcomes for participants in the SIMPLIFY-1 and SIMPLIFY-2 trials as well as the extended-access protocol. They concluded that momelotinib delivered durable benefits.

For patients treated during SIMPLIFY-1, the median overall survival (OS) after follow-up of nearly 5 years was 53.1 months for those who received ruxolitinib in the first line and then crossed over to momelotinib after 24 weeks, but it was not reached among patients originally treated with momelotinib (HR, 0.99; P = .97).

Among SIMPLIFY-2 participants, the median OS for patients treated first with ruxolitinib or best available therapy who then crossed over to momelotinib was 37.5 months compared with 34.3 months for those originally randomized to receive momelotinib (HR, 0.96; P = .86). The momelotinib findings compare favorably with previously reported median OS ranging from 13 to 30 months in patients who have discontinued ruxolitinib, investigators said.

In terms of spleen response, 27% of patients in the momelotinib group and 29% in the ruxolitinib cohort in SIMPLIFY-1 achieved a reduction in spleen volume of 35% or more by week 24 (noninferiority P < .001). Overall, 40% of patients randomized to momelotinib achieved a splenic response at any time during the study.

In both trials, the proportion of patients able to achieve TI at week 24 for momelotinib compared with ruxolitinib or best available therapy, respectively, was 67% versus 49% (P = .001) in SIMPLIFY-1 and 43% versus 21% (P = .001) in SIMPLIFY-2.

Investigators also examined symptom-related outcomes for patients in the thrombocytopenia and intention-to-treat populations in the SIMPLIFY trials in a separate retrospective analysis also presented at ASH 2020.10

In SIMPLIFY-1, the TSS response rate with momelotinib versus ruxolitinib, respectively, was 28% versus 33% for those with a baseline platelet count of less than 150 x 10^9/L and 28% versus 41% for the overall population. In SIMPLIFY-2, the TSS rates were higher across platelet levels for momelotinib versus ruxolitinib: 24% versus 3%, respectively, for those with platelet counts of 150 x 10^9/L or lower, and 26% versus 6% overall.

Moreover, the rates of treatment-emergent adverse effects with momelotinib therapy were similar among patients with platelet levels lower than 150 x 10^9/L and in the overall populations in both studies, although nausea, fatigue, and anemia were more common in those with lower platelet levels.

“These analyses demonstrate that momelotinib safety and activity profile do not appear to be affected by baseline platelet count,” Jean-Jacques Kiladjian, MD, PhD, head of the Clinical Investigation Center at Saint Louis Hospital in Paris, France, said while presenting the data. "In contrast, activity with ruxolitinib declined in patients with lower platelets."
Fixed-Dose Pertuzumab/Trastuzumab Combo Provides New Option in HER2+ Breast Cancer

by ERICA DINAPOLI

A MAINTENANCE FIXED-DOSE, subcutaneous (SC) combination of pertuzumab (Perjeta) and trastuzumab (Herceptin) with hyaluronidase-zzxf (Phesgo) offers an outpatient option for patients, according to Antoinette R. Tan, MD.

Results from the phase 3 FeDeriCa trial (NCT03493854) showed that the combination demonstrated noninferiority to intravenous (IV) formulations of the 2 drugs with regard to pharmacokinetics, clinical efficacy, and safety.1 These findings led to the FDA approval of the fixed-dose therapy for patients with early and metastatic HER2-positive breast cancer on June 29, 2020 (TABLE).

The global, multicenter, open-label, randomized phase 3 trial, which enrolled 500 patients, met its primary end point after demonstrating noninferiority on the basis of predose cycle 8 P serum trough concentration (Ctough) for the pertuzumab component of the fixed-dose combination. Moreover, noninferiority for the predose cycle 8 serum Ctough was also demonstrated for the trastuzumab component of the SC combination compared with IV trastuzumab.

Notably, the total pathological complete response in the breast and axilla, along with the safety profile, was found to be comparable between the 2 treatment regimens.

Regarding safety, common adverse effects (AEs) observed with the SC combination included alopecia, nausea, diarrhea, anemia, and asthenia. The combination can also lead to worsening of chemotherapy-induced neutropenia, according to the FDA.2

“The fixed-dose combination of SC pertuzumab and trastuzumab offers a faster and more convenient treatment option for patients with HER2-positive breast cancer compared with intravenous infusions,” Tan said. “Several benefits are associated with this SC administered product, such as less time spent in treatment chairs and infusion centers, which is a critical quality-of-life factor.”

The regimen could offer patients an opportunity to continue administration at home by a qualified health care professional following initial treatment in combination with IV chemotherapy. Developing an at home administration protocol for the SC formulation is an important area of future research, Tan added.

Tan is chief of Breast Medical Oncology and codirector of the Phase I Program at the Levine Cancer Institute of Atrium Health. In an interview with OncLive OnAir, an OncLive® podcast, she spotlighted the FDA approval of the fixed-dose combination of SC pertuzumab and trastuzumab with hyaluronidase, in combination with IV chemotherapy, along with the significance of the approval in the HER2-positive treatment paradigm.

Please discuss the benefits of the combination versus the standard regimen?

The treatment of patients with HER2-positive breast cancer with intravenous pertuzumab and chemotherapy has been considered a standard of care in the neoadjuvant and adjuvant settings, as well as in the first-line setting, in advanced HER2-positive breast cancer.

However, for many patients, the long infusion times, along with the need for repeated invasive IV access, are inconvenient aspects of the treatment experience. Additionally, increased use of IV-administered agents in oncology has placed a strain on medical centers with respect to the time and resources required to prepare and administer such infusions. As such, the switch to the subcutaneous route of administration for monoclonal antibodies such as trastuzumab, has been demonstrated to reduce the treatment burden for patients while improving time and resource utilization at a treatment facility.

The new SC formulation, which combined the 2 monoclonal antibodies trastuzumab and pertuzumab with the recombinant human hyaluronidase in 1 vial, was developed. Unlike the IV formulation of trastuzumab, dosing with this SC fixed-dose formulation is not dependent on the patient’s body weight. Also, the fixed-dose combination of pertuzumab and

CONTINUED ON PAGE 54
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trastuzumab is administered in about 5 to 8 minutes as opposed to the 150 minutes it would take for an IV infusion of the loading dose of each of the 2 medicines given sequentially, followed by 30 to 90 minutes for each IV administration of the maintenance doses. The new SC formulation improves the treatment experience by lessening the time associated with administration.

Could you speak to how the design of the FeDeriCa trial resulted in this regulatory decision?

Eligible patients [enrolled to the FeDeriCa trial] included those who had HER2-positive invasive breast cancer with a tumor that was greater than 2 cm or who had node-positive disease. Mostly patients with stage II/III breast cancer were included. These patients were randomized 1:1 to receive IV pertuzumab and trastuzumab or the fixed-dose SC combination injection. Both were administered every 3 weeks with neoadjuvant chemotherapy.

Following surgery, the patients continued adjuvant HER2-targeted treatment per their randomization. The chemotherapy backbone was either dose-dense doxorubicin and cyclophosphamide for 4 cycles, followed by weekly paclitaxel for 12 weeks, or doxorubicin and cyclophosphamide every 3 weeks for 4 cycles, followed by docetaxel every 3 weeks for 4 cycles. The choice between the chemotherapy regimen options [was based on the] investigator’s discretion prior to randomization.

I want to highlight the efficacy observed in terms of the pathologic complete response rate, meaning no tumor in the breast and lymph nodes; these rates were nearly identical in both arms at about 60% and proved to be comparable to [what has been seen in] other neoadjuvant trials with HER2-targeted therapy.

The SC injection, in combination with chemotherapy, also demonstrated noninferior trough concentrations of pertuzumab, when compared with IV trastuzumab and pertuzumab, in combination with chemotherapy, in patients with early-stage HER2-positive breast cancer.

What safety signals were observed with the SC combination?

We saw comparable safety profiles [between the 2 approaches]. No new or unexpected toxicities were observed. The most common grade 3/4 AEs with the fixed-dose combination included neutropenia, low white blood cell count, and diarrhea, but these toxicities were expected. The incidence rates of primary and secondary cardiac AEs were low in both arms and were pretty consistent with rates reported in previous studies with similar treatment regimens.

As with any SC product, there can be injection site reactions; however, in the SC arm, [the rate of these reactions] was low. About 13% of patients experienced low-grade symptoms such as pain, burning, or redness at the injection site.

What were the clinical implications of these findings?

Other than spending less time in treatment chairs, another benefit [of the SC administration] is the increased capacity of infusion chairs [in cancer centers]. This will create greater availability for patients who can only receive IV therapy. Furthermore, there’s shorter administration time, which allows for greater flexibility [for patients].

There’s also the potential to reduce drug delivery, health care costs, as well as pharmacy and nursing resource use. An SC-administered product would involve shorter preparation time and shorter administration time. From a patient perspective, there could potentially be less pain and discomfort because they wouldn’t need IV access. This [approach] will also help preserve their veins.

In light of the coronavirus disease 2019 (COVID-19) pandemic, how could this regimen minimize the risk of contracting the virus?

When you consider the current state of the COVID-19 pandemic, having an SC medication [that can potentially be] administered by a health care worker, such as a home health nurse, is very appealing because this could save patients a trip to the cancer center.

Where should future efforts be focused with regard to this approach?

Developing an at-home administration protocol for the SC formulation is an important area of future research. It could provide many advantages to both patients and infusion centers alike-especially during the COVID-19 pandemic. However, we must proceed cautiously. Specific protocols are required to ensure the setup is safe and it must be rigorously evaluated prior to implementation.

This strategy is actually being evaluated in a single-arm, multicenter, expanded-access study [that is being done in an attempt] to provide at-home SC administration of pertuzumab and trastuzumab fixed-dose combination [NCT04395508].

This study will enroll approximately 400 patients with HER2-positive breast cancer who are currently receiving IV pertuzumab and trastuzumab. An at-home health nursing provider will administer the fixed-dose of SC pertuzumab and trastuzumab from the patient’s homes. This is an important clinical trial effort that will assess whether this approach is feasible and safe.

What emerging agents under exploration do you find most exciting?

Several compounds are currently under clinical development, including novel ADCs [antibody-drug conjugates] that look promising. One agent it SYD985, which is an ADC composed of trastuzumab, linked to duocarmazine. The other emerging HER2-targeting ADCs, XMT-1522 and ARX788, are still in early-phase research. XMT-1522 is a human IgG1 anti-HER2 monoclonal antibody with a cytotoxic payload called auristatin F-hydroxypropylamide. ARX788 is another HER2-targeted antibody site, specifically conjugated to a different cytotoxic moiety called Amberstatin269, which is a tubulin inhibitor. It’s very exciting to see the development of this class of drugs.

REFERENCES


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When Payers’ “Cost-Saving” Steps Don’t Help Patients

by MARY CAFFREY

WHITE-BAGGING. BROWN-BAGGING.

Step therapy. Home infusion. Each term in the roster of payer cost-saving strategies means something different, but for the panelists taking part in an October 28, 2020, session at the Community Oncology Alliance (COA) Payer Exchange Summit, the bottom line was the same: Taking control away from oncologists can lead to waste, cost patients time and money, and be downright dangerous.

COA Executive Director Ted Okon, MBA, moderated the panel featuring Michael Diaz, MD, director of patient advocacy, Florida Cancer Specialists & Research Institute; Janelle Hamilton, compliance officer and director of payer relations, Illinois Cancer Care, PC; and Barbara McAneny, MD, chief executive officer, New Mexico Hematology Consultants, Ltd.

With Diaz, the current president of COA, and McAneny, a recent president of the American Medical Association, on the panel, no one held back their thoughts on how cost-saving efforts, however well-intentioned, can backfire and do harm.

The panel reviewed these strategies:

• **White-bagging** refers to specialty pharmacies sending prefilled oncology therapeutics directly to the oncology practice; thus, if the physician needs to adjust the dose, the drug must be shipped back to the pharmacy.

• **Brown-bagging** occurs when drugs are sent directly to the patient, who must store them properly and bring them to the physician’s office to be administered.

• **Step therapy** requires patients in commercial and some Medicare Advantage plans to take oncology drugs or supportive therapies that may not be what their doctor prescribes, to check that they do not work before the preferred treatment is dispensed.

• **Home infusion** calls for oncology drugs to be given outside an infusion center, by a nurse who may or may not be a certified oncology nurse. The physicians on the panel objected strongly to this practice, because they said an unaccompanied nurse is not equipped to manage an adverse reaction that could take place at the time of administration.

McAneny addressed problems with white-bagging, especially when the oncologist needs to adjust a patient’s regimen. “The issue with white-bagging is that if the insurance company has sent me that drug and that dose, and I need to change that patient’s dose for any reason—or even change to another regimen altogether, because the patient has progressed or isn’t tolerating the first regimen—then I have to send that patient away, and bear the cost of sending that drug back to whoever sent it to me. And then the patient would have to wait until the new drug is approved and has come in, and then make another trip [to pick it up],” she said.

McAneny, who noted that she has patients who may be traveling 100 miles to see her, said this is costly to patients and caregivers. “Something that needs to be considered—something that’s almost never considered when insurers are making these changes—is the effect on the patient’s out-of-pocket expense... If that patient has to [leave] and come back another day, then, for instance, their daughter [who accompanies them] may have to take another day out of work, again; or maybe a kid has to be taken out of school, again; or they have to make other arrangements to get transportation,” she emphasized. “It really is going to increase the inequities that we see for poor people versus wealthier people.”

In addition, when oncologists cannot manage the drugs themselves, they don’t know who has mixed it, or whether it’s been kept at the right temperature during shipment, McAneny said. “I think this is an example of an insurance company sacrificing patient safety,” she stressed. “It’s for expediency, and the hope that this will somehow save them money.”

Brown-bagging is even worse, she said, because patients can leave drugs in their car where they are exposed to heat.

Hamiton said that physicians in her practice reach patients by traveling to rural areas of Illinois once a week. “So, if that drug is not there, or that dosage changes, and we’re not back in that clinic for another week, we stand to delay that treatment,” she said, adding that she’s succeeded in changing 1 payer contract to allow the clinic’s physicians to buy-and-bill to avoid this circumstance. But that’s just 1 contract.

Diaz said the situation threatens the trust that doctors work to establish with patients. Both doctors and patients, he said, “want to get their value, but they’re also concerned about safety.”

CONTINUED ON PAGE 58 ▶
The ELAINE Study is evaluating an investigational oral drug in postmenopausal women with ER+/HER2-breast cancer whose disease has shown progression on previous AI treatment in combination with a CDK 4/6 inhibitor and with an acquired estrogen receptor 1 (ESR1) mutation.*

Patients may qualify to participate in the study if they:
• Are postmenopausal
• Have been diagnosed with locally advanced or metastatic ER+/HER2-breast cancer
• Have been diagnosed with an acquired ESR1 mutation. This may have been detected in previous testing and if not, a blood test as part of the study will be done to see if the mutation is present
• Had disease progression after taking an AI in combination with a CDK 4/6 inhibitor*

Patients who pre-qualify based on inclusion and exclusion criteria will receive a liquid biopsy blood test at no cost to determine if an acquired ESR1 mutation is present prior to participation in the study.

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*AIs include Arimidex (anastrozole), Femara (letrozole), or Aromasin (exemestane). CDK 4/6 inhibitors include Kisqali (ribociclib), Ibrance (palbociclib), and Verzenio (abemaciclib).
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ER, estrogen receptor; HER, human epidermal receptor.

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Diaz related the story of one patient who, unbeknownst to his Florida clinic, told the mail-order pharmacy to stop sending his oral medication with a cold pack, and the clinic started seeing detectable levels of cancer in his bloodwork. Patients assume the insurer always does things that are in their interest, but that’s not always the case, Diaz said.

McAneny said the mail-order system leads to waste, because patients often continue to receive drugs after their regimen or dose has changed. At her New Mexico clinic, McAneny instructs patients to bring unneeded therapies to her office—and one time, she took the wasted treatments to a meeting with a payer to make a point.

“I took that box with me and I dumped it out on the desk and said, ‘Here’s $300,000 worth of drugs that you paid for, that our patients could not take.’ And they decided that maybe they would let us buy-and-bill and supply those medications,” McAneny said.

Okon and Diaz then discussed problems with step therapy. “I never want to say ‘step therapy’ without saying ‘fail first.’ Because that’s what step therapy is,” exclaimed Okon. He said the use of step therapy has expanded beyond its original intent, with pharmacy benefit managers dictating which drug must be used. Diaz called it “practicing medicine without a license.”

Step therapy is especially problematic when patients are denied supportive treatments to control pain or nausea, or forced to take therapies that are more toxic. “We have a hard time managing pain anyway,” Hamilton said. “And a delay to get adequate pain control because you’re limited to [a certain drug] you can start with, and to the amount of drug, has been an issue.”

Payers have put mandates on sleeping medications, anticoagulants, and required iron formulations, meaning 10 trips to the clinic can be required instead of 2, the panelists said. The inconvenience of the patient isn’t taken into account, they said. Diaz said some payers literally require patients to violently throw up before they will cover medication to prevent nausea. Yet physicians know that if patients who are likely to become ill don’t get this preventive treatment up front, there’s a good chance they might not choose to get any more chemotherapy.

Besides being costly to practices, McAneny said putting physicians through these hoops contributes to burnout. “Something that we’ve seen across the country is that physicians would like to spend more time with patients. Yet we know that for every hour they spend with patients, they get to spend 2 hours with a computer. And now they probably get to spend another half-hour talking to someone who knows nothing sometimes about oncology and is just reciting the payer’s policy from their manual to you,” she said.

“These policies are incredibly shortsighted,” McAneny continued, noting the growing shortage of oncologists. “The payers are [interested in] short-term profits, perhaps short-term savings, at the cost of a long-term negative impact on the health care delivery system.”

Home infusion was controversial before coronavirus disease 2019, but it has gained attention because some payers have promoted it as a way to keep patients from traveling to infusion centers. McAneny believes this, too, is shortsighted. A patient’s bedroom or bathroom is likely not as sterile as an infusion center, and there’s no way of knowing if a nurse is entering a house where someone has been exposed to the virus.

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### More Insurers Are Entering ACA Marketplaces

by **KEITH A. REYNOLDS**

MORE INSURANCE COMPANIES ARE entering Affordable Care Act (ACA) marketplaces, bringing more options for patients.

According to an analysis from the Kaiser Family Foundation, this is the third straight year that insurers are entering the marketplaces and expanding their services. Specifically, 30 insurers joined the marketplaces across 20 states, and an additional 61 insurers expanded their services within states they already serve. More than one-third of counties (approximately 38%) will have more insurers serving their marketplaces, and only 0.4% will see a net decrease.

These moves by insurance companies over the past several years have sharply increased the number of options available to patients. Approximately 78% of marketplace enrollees, versus 48% in 2018, will be able to choose from at least 3 insurers; only 3% of enrollees, versus 26% in 2018, will have a single insurer serving their county (FIGURE). The amount of insurer participation varies greatly within states, and rural areas tend to have fewer insurers than metropolitan areas.

Insurer participation levels have steadily climbed back to levels seen in the early years of ACA implementation. In 2014, an average of 5 insurers participated in each state’s ACA marketplace. In 2017, insurance company losses led to a number of high-profile exits from the market, and the average number of companies per state decreased to 4.3. In 2018 insurer participation dropped even further, averaging 3.5 per state.

“The share of marketplace enrollees with only 1 insurer option (3%) has continued to decrease and will be the lowest rate since 2016 (when 2% of enrollees had only 1 insurer option),” McDermott et al wrote. “As has been the case in the previous 2 years, [a number of companies are] entering the market or expanding their footprints within states in 2021.”

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### Reference


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### Figure

**FIGURE.** Marketplace Enrollees Will Have More Options in 2021 as Insurers Expand Service Areas

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Adult Nonmalignant Hematology Is an Endangered Field That Merits Protection

by JENNIFER R. GREEN, MD

HEMATOLOGISTS USE THE TERMS classical, nonmalignant, and benign hematology to reference the same entity: the study and management of nonmalignant disorders of the blood. It is a discipline unto itself, distinct from its sister field, malignant hematology. The scope of practice can be broad and includes thrombotic and hemorrhagic disorders, transfusion medicine, hemoglobin disorders including sickle cell disease and thalassemia, anemia, thrombocytopenia, leukocytosis, leukopenia, and disorders of iron metabolism.

In many health care systems, classical hematologists function as stewards of cost-intensive, specialty-related medications that are often complex and require content knowledge, experience, and clinical expertise for appropriate management. Others find roles as systems-based hematologists, defined as a specialty-trained physician, employed by a hospital medical center or a health system, who optimizes individual patient care as well as the overall system of health care delivery for patients with blood disorders. Duties of these professionals can include implementing health care initiatives for the management of thrombosis or bleeding, working in conjunction with anticoagulation oversight clinics, and standardizing management of therapeutic phlebotomy.

To characterize the future of the workforce for this diverse field, results of an American Society of Hematology (ASH) survey of practicing hematologists projected that nearly 25% of hematologists specializing in nonmalignant disorders would reach retirement age by 2018. This was expected to have a profound impact on creating a workplace shortage. The study results cited several influences, including the age of the workforce and decreasing rates of graduate selection of nonmalignant hematology as a primary area of focus. Other influences included salary discrepancies between nonmalignant hematology and malignant hematology/oncology, lack of mentorship, and uncertainty regarding nonmalignant hematology job opportunities in nonacademic settings. Physicians practicing in adult nonmalignant hematology disorders are now seeing the results of this decreasing specialist collective in clinical care and research.

Educational programs have historically been tasked with attempts to address the shrinking pool of classical hematologists. Prior research showed that only 20% of hematology/oncology fellowship graduates pursued an academic career with a clinical research focus, and only 8% pursued an academic career as a clinician-educator. Of the 20%, less than 6% selected careers in nonmalignant hematology. A great demand exists for well-trained physicians. Furthermore, literature suggests that soon a large patient volume with hematology care needs will be without a sufficient number of specialists.

These challenges may require complex solutions (FIGURE). One initiative is an expansion of easily accessible nonmalignant hematology training and educational resources for both trainees and practicing hematologists/oncologists. Many colleagues have not experienced the opportunity to train with a dedicated mentor in this specialty, as fellowship programs can vary significantly in their faculty experience with nonmalignant hematology. In fact, many programs have few available dedicated hematologists on staff for teaching and clinical care. Guidance and widely disseminated education can enhance practitioner comfort in the management of hematologic conditions when programs do not have an available content area expert.

Additional focus should be given to the enlistment and training from colleagues to surmount this disparity. Offering training sessions or workshops in the management of high-yield, common topics led by experienced hematology teachers for their colleagues in internal medicine, family practice, and primary care could provide a foundation for initial management of hematologic issues, improved comfort with the subject matter, and an enhanced understanding of the indications for specialist referral. Topics of interest include management of iron-deficiency anemia, simple and complex thromboses, anticoagulation oversight, bleeding evaluations, thrombotic microangiopathy presentation and identification, and the initial evaluation of cytopenias. These examples represent common scenarios with significant intersection with classical hematology.

Residency training programs may also find the opportunity to incorporate nonmalignant hematology focus into their curricula. Not only would this serve to improve proficiency and prepare trainees for the reality of their work, but to also provide a foundation to encourage a future career in this vital field.
Institute for Health Workforce Equity, and it has raised awareness through publication and educational initiatives.\(^2,3,10\) In October 2020, ASH announced that it will provide “institutional funding to develop 10 new innovative hematology-focused fellowship tracks within existing adult hematology-oncology training programs.”\(^9,10\) The training provided in the educational platform must lead to eligibility for American Board of Internal Medicine hematology certification. The goal of the program is to generate enough recruitment and training to add at least 50 academic hematologists in the coming years, with a focus on training hematologists in nonmalignant disorders.\(^10\) More information will follow when the request for proposals becomes available on February 15, 2021. Additional information is available at https://bit.ly/37Gmyic.

Well-informed hematologists/oncologists can also play a critical role in reshaping the trajectory of these gaps through raising awareness, participating in professional societies and continuing medical education, teaching students and trainees, and recruiting colleagues to extend these efforts. The nurture and retention of nonmalignant hematology content expertise is a critical aspect of health care that merits protection.

### REFERENCES


HER2-Directed Antibody-Drug Conjugates May Carve Out a Place in NSCLC Landscape

by BRITTANY LOVELY

THE CURRENT STANDARD OF care for patients with non–small cell lung cancer (NSCLC) does not include therapies targeting HER2, a mutation that occurs in up to 4% of cases. However, data from recent studies of antibody-drug conjugates (ADCs) directed at HER2 activity are generating excitement about the potential utility of ADCs in this space. Specifically, efficacy data from phase 2 trials have described HER2 gene mutations as an emerging biomarker to identify therapies for patients with metastatic disease (TABLE 1-2).1-3

Ado-trastuzumab emtansine (T-DM1; Kadcyla) broke the historical trend of low response rates to HER2-directed therapies in lung cancer with data from a phase 2 basket trial (NCT02675829), which examined the ADC in a cohort of patients with advanced HER2-mutant lung adenocarcinoma. The objective response rate (ORR) among 18 patients with HER2 mutations was 44% (95% CI, 22%-69%), all partial and confirmed responses. The median progression-free survival (PFS) for all patients in the cohort was 5 months (95% CI, 3-9), whereas the median PFS for responders was 6 months (95% CI, 4-not reached).1

Data from DESTINY-Lung01 (NCT03505710), a phase 2 trial involving the ADC fam-trastuzumab deruxtecan-nxki (Enhertu), further solidified the potential role of these agents in patients with HER2-mutant disease. An interim analysis presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program (2020 ASCO) showed an ORR of 61.9% (95% CI, 45.6%-76.4%) in 42 patients with unresectable/metastatic nonsquamous NSCLC treated with trastuzumab deruxtecan.2 Further, the median PFS was 14 months (95% CI, 6.4-14.0), and median overall survival was not reached (95% CI, 11.8-not reached).

“Antibody-drug conjugates are showing promising data in breast cancer, and some of that efficacy has been observed in data in lung cancer,” said Hossein Borghaei, DO, MS, during an OncLive® Lung Cancer Talk video program.

Borghaei was joined by Balazs Halmos, MD, MS; Jarushka Naidoo, MBBCh; and Joshua M. Bauml, MD, in reviewing the latest data that pave a path forward for the role of HER2-targeted agents for patients with metastatic lung cancer.

The methods for establishing the most effective biomarker for HER2-targeted therapies were a key focus in the discussion. Whereas HER2 positivity has been defined by immunohistochemistry (IHC) protein
expression (IHC 3+ or IHC 2+) for breast cancer therapy, emerging data in NSCLC are identifying responses in patients with HER2 activating mutations through molecular analysis of tissue samples.²³ Borghaei estimated the rate of HER2 mutations in NSCLC at 2% to 4% and HER2 overexpression by IHC testing at up to 30%.

**NOVEL COMPOUNDS LEAVE AN IMPRESSION**

**BORGHAEI** Trastuzumab deruxtecan seems to be garnering a lot of attention, primarily because it has received breakthrough therapy designation from the FDA in NSCLC, and it’s already approved in breast [and gastric] cancers.

At the 2020 ASCO meeting, data were presented from a phase 2 study that investigated the utility of the compound in patients with NSCLC and a HER2 mutation. Keep in mind this is not the IHC overexpression that we were talking about; this is strictly the HER2-mutated NSCLC. Patients who participated in this study had received prior chemotherapy, and the majority had received chemotherapy plus immunotherapy.

The patient population was very similar to that of other NSCLC studies that we’ve seen in this setting. Interestingly, based on a 42-patient data set, a response rate of nearly 62% was reported, which is pretty eye-catching. The median duration of response was not reached at the time of the initial presentation. It looks like a very active, very interesting compound.

There is a specific toxicity that I think we should discuss. With this compound you do have to worry about interstitial lung disease or pneumonitis because it can happen, and learning how to mitigate some of that is important to clearing the established safety of the compound and, of course, making sure that patients are identified if they have that.

The median PFS was around 14 months, which was pretty interesting for a patient population that’s already been treated. So it does appear that we’re making some progress. ADCs, at least with this particular compound, seem to be very promising, and subsequent studies are needed to establish their role.

Based on these efficacy data, do we move this agent to the front line? Or is this compound strictly for patients who’ve had chemoimmunotherapy? I think subsequent studies are going to [evaluate] the importance of establishing a role for these kinds of compounds.

**BAUML** This is a very interesting situation because in contrast with RET inhibitors, for instance, these drugs—both T-DM1 and trastuzumab deruxtecan—are already approved by the FDA in other indications such as breast cancer; you can access them.

So if you have a patient who comes in with a HER2 exon 20 mutation, what are you doing now? If you have access to a clinical trial, I’m sure that’s what you’re selecting for your patient.

But if you don’t enroll on a trial and that patient comes to your door, Dr Naidoo, what are you doing?

**NAIDOO** I present both options [T-DM1 and trastuzumab deruxtecan] to the patient, and I print it out on paper and go through it with them. Now, usually their eyes glaze over a little bit, I have to admit, and at the end they might say, “What would you do if you were me?” But I feel better showing them what the 2 options are and saying I don’t clearly know which one may be better for you, but I will balance my decision, taking their comorbidities into account as well as various other things. I think that is the fairest way to approach it.

I have a lot more clinical experience with T-DM1. I’ve given it to patients with NSCLC with HER2 aberrations for several years, and in a past life, when I treated patients with breast cancer, I had certainly given T-DM1.

I think there is a certain level of clinical familiarity that providers are probably going to have that may sway them in the direction of T-DM1. However, when we have a very exciting agent with a very impressive response rate, and when the phase 2 data that supported the use of T-DM1 do not look as impressive as those for trastuzumab deruxtecan, I think that that may change over time.

**BAUML** When you’re using T-DM1 or trastuzumab deruxtecan, are you using them after chemoimmunotherapy? Are you using them in the first line? How are you approaching that?

**NAIDOO** Again, it’s a similar approach to a RET inhibitor. I’m a believer that oncogenic drivers are driving the growth of the cancer. If a patient is stable and can wait for the results of testing, I would prefer to give it in the first line.

**BAUML** Interesting. Dr Halmos, where are you using these agents right now?

**HALMOS** I think we need to learn a little bit more in this setting. I don’t think I’m fully comfortable using them in the first line yet, especially, for example,
in HER2-mutated disease because of the bad pneumonitis. There’s that risk—how is it going to play out?

It’s such a complex molecule, and as a result, there’s a lot of nuance. I think I would love to learn a little more about it before replacing a fairly effective treatment up front for most of our patients with metastatic lung cancer, and that is chemotherapy.

I would sequence them more in the second-line setting, but I am very eager to learn more about these compounds, including TKIs [tyrosine kinase inhibitors] that are moving along in the HER2 field, as well.

BORGHAEI: What I like about ADCs is that if we can establish that by detecting the HER2 overexpression using IHC, we can actually show clinical utility.

If an ADC works the way it’s promised—the antibody moiety binds to HER2, as long as it’s overexpressed—and is internalized and goes to the target, it could potentially have a lot more utility. Unless there are specific mutations that prevent internalization, or if the cancer cell is inherently resistant to the protection of chemotherapy that’s being used as a toxic payload, the clinical utility of the agent can be expanded a little.

I think these are important topics to explore in the future studies. In fact, the study that we’re running will test this particular compound [trastuzumab deruxtecan] in both patients with a HER2 mutation and those with HER2 overexpression. We should be able to generate some data in these settings to see where the clinical utility really lies [NCT04042701].

BAUML: What’s fascinating about these agents is that these ADCs are gigantic molecules; they are huge. So it is not expected that they’re going to penetrate the CNS [central nervous system]; it is not expected they are going to be getting into the cells.

But what’s remarkable, in a paper about T-DM1, Li et al did an enormously elegant analysis where they looked at what factors lead to response. Investigators performed IHC, FISH [fluorescence in situ hybridization], mass spectroscopy, and mutation analysis, and the only thing associated with response was mutation, which shouldn’t be the case.

It should not make any sense given how these drugs work, and yet that is exactly what we see. I wonder with trastuzumab deruxtecan—which has a much higher response rate, a much longer durable response—whether we’re still going to see that same thing. But what I took away from the toxicity profile of trastuzumab deruxtecan is that it looks a lot like chemotherapy. Although it is a targeted agent, the adverse effect profile looks similar to that of a platinum doublet.

BORGHAEI: But that’s not unprecedented. We’ve seen other ADCs that have similar profiles because the toxic payload is basically cytotoxic as you get it into. Now, I’ve seen the data for patients with a HER2 mutation, and in terms of predicting responsiveness, I’m also a little puzzled to the extent that I’m trying to communicate with the investigators about how to best explain a drug that’s supposed to bind to a specific target.

Why is it that in a patient with a HER2 mutation, it actually does seem to be working better? I don’t think there is any clear evidence at this point, at least not an explanation that I have seen, that’s satisfactory. I’ve seen the same data, and yes, I do question them. It’s an ADC; the simple mechanism is supposed to be the antibody binds the target, it’s internalized, the toxin is released, and you get your activity. But unfortunately, the patients experience some adverse effects because the drug does get out into the systemic circulation.

HALMOS: Let me mention that this highlights how much we don’t know about HER2 expression and HER2 amplification in lung cancer. It’s one thing for a subset of patients who have a mutation that is oncogenic, actionable, and important for the cancer to survive to have that identified pathway. But for those who have HER2 overexpression, resistance may emerge within weeks or as selection of subclones that don’t express it. So any long-term mutation to the compound is simply not realistic.

NAIDOO: I think on that, as well, the mutation matters. Similarly, the paper you referenced, as well as other work, has shown that patients with exon 20 TYMA insertions appear to have poorer responses. So obviously having a familiarity with exactly what you’re treating is the first step.

BAUML: Maybe the HER2 mutation predicts the binding specificity, or it somehow affects weak or stronger binding, depending on the kind of mutation. Maybe it has something to do with that, and again, as was pointed out, we simply don’t understand much of it. Clinical development is a lot faster than the science.

Usually we have a little more science than clinical development, and here the drugs are working, we’re trying to use them, but we don’t understand what exactly is going on from a science point of view.

REFERENCES

MORE ON OncLive.com
Experts Review Key Lung Cancer Data from the 2020 ASCO Virtual Scientific Program
Watch the entire edition of The Talk for more on metastatic non–small cell lung cancer, including a number of exciting new available therapies and results of key datasets presented as part of the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program. Hossein Borghaei, DO, MS, Balazs Halmos, MD, MS; Jarushka Naidoo, MBCH; and Joshua M. Bauml, MD, discuss the impact these data have on clinical decision-making and treatment selection for patients.

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RENAL CELL CARCINOMA (RCC) is the most common type of kidney cancer. In 2019, 73,820 patients received a diagnosis of kidney cancer according to data from the American Cancer Society. Of those patients, roughly 30% to 35% present with de novo metastatic disease, and a subset of patients with localized disease subsequently develop metastatic disease. The multidisciplinary management of advanced RCC has undergone tremendous changes over the past several years. In 2005, the targeted therapy era was launched with the introduction of VEGF- and mTOR-targeted therapies. Most recently, immunotherapy (IO) has entered the treatment landscape, initially as single agents and now in combination with other IOs and also VEGF-targeted therapies. Additionally, the role of up-front cytoreductive nephrectomy (CN) has been evolving in advanced disease.

RISK STRATIFICATION FOR PATIENTS WITH ADVANCED DISEASE

The most commonly used risk classification system is the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, which was developed and validated in the era of tyrosine kinase inhibitors (TKI).

CYTOREDUCTIVE NEPHRECTOMY

The role of CN in the setting of metastatic disease remains controversial. One of the first descriptions of CN in this setting was in a series of 33 patients in 1967 by Milton et al. From that time, the role of CN grew and was tested in the setting of cytokine therapy in 2 randomized controlled trials (RCTs). In both trials, patients were randomized to receive either interferon α (IFN-α) alone or CN followed by IFN-α. In a combined analysis of 331 patients from both trials, CN was associated with improved overall survival (OS; 13.6 vs 7.8 months, respectively; \( P < .01 \)). However, the trials were criticized for their modest survival benefit and imbalance between treatment groups. Moreover, IFN-α was shown to have severe adverse effects (AEs) and was not widely used at that time.

More recently, 2 RCTs evaluated the role of CN in the context of targeted therapy use with sunitinib (Sutent). Although these trials have their limitations, their data have provided instruction regarding the utility of CN in advanced disease.

CARMENA

Investigators of the prospective phase 3 noninferiority CARMENA trial (NCT00930033) randomized patients to CN followed by sunitinib versus sunitinib alone if they had intermediate- or poor-risk disease. This model was developed in the cytokine era and is less commonly applied now. Investigators have validated both models in numerous studies.

Frontline Planning for Metastatic RCC Undergoes Change

by JUAN JAVIER-DESLOGES, MD, MS; ITHAAR DERWEESH, MD; AND RANA R. MCKAY, MD

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results presented at the 2019 Genitourinary Cancers Symposium restratified patients using IMDC criteria. The results demonstrated a clear benefit for the sunitinib-alone arm versus CN then sunitinib for patients with 2 IMDC risk factors (31.2 vs 17.6 months, respectively; \( P = .03 \)). They also showed that in the sunitinib-alone arm a subset of patients went on to receive CN, and those patients had a longer median OS compared with those receiving only sunitinib of 48.5 months (95% CI, 27.9-64.4) versus 15.7 months (95% CI, 13.3-20.5). Together, these results support the use of up-front systemic therapy and the hypothesis that some carefully selected patients may benefit from CN.

**SURTIME**

In a second illustrative RCT, investigators of SURTIME (NCT01099423) evaluated immediate CN followed by sunitinib versus sunitinib followed by delayed CN. In the intention-to-treat population, OS was significantly higher in the deferred CN group compared with the immediate CN group (HR, 0.57; 95% CI, 0.34-0.95; \( P = .03 \)). Similar to CARMENA, the study drew criticism for its slow and poor accrual. The gradual accrual led investigators to modify the primary end point to an intention-to-treat, 28-week progression-free rate (PFR) instead of progression-free survival (PFS). Nevertheless, both trials provide level 1 evidence indicating a need for systemic therapy and that the use of CN requires careful patient selection. \(^{13} \)

Additional studies hope to further clarify the answer regarding CN’s role in the setting of metastatic RCC. NORDIC SUN (NCT03977571) is an RCT of intermediate- and poor-risk patients receiving checkpoint IO. After 3 months or a total of 4 doses of nivolumab (Opdivo) combined with ipilimumab (Yervoy), whichever comes first, patients will be evaluated for resectability at a multidisciplinary meeting. Those with at least 3 IMDC risk factors who are deemed suitable for CN will then undergo randomization. \(^{14} \)

At the forefront of trials in the development of CN’s role, there are 2 additionally important studies. The PROBE trial (NCT04510597) will evaluate up-front IO therapy for patients with metastatic RCC, and those who have a complete response, partial response, or stable disease will be randomized to CN or continue systemic therapy alone. \(^{15} \) Investigators of the CYTOSHRINK trial (NCT04090710) will evaluate stereotactic body radiation therapy (SBRT) with or without nivolumab plus ipilimumab in patients with intermediate- and poor-risk disease. These more contemporary studies will evaluate the role of surgery or SBRT in the primary treatment of renal tumors in patients with advanced disease receiving modern therapy. \(^{16} \)

**COMBINATION THERAPY**

Until 2018, treatment with a single-agent TKI was the standard of care for patients with advanced RCC. In 2018, a significant transition in the treatment paradigm occurred in the frontline setting for these patients. The CheckMate 214 trial (NCT02231749) compared nivolumab/ipilimumab with sunitinib and demonstrated improved 18-month OS (75% vs 60%), improved PFS (11.6 vs 8.4 months; \( P = .03 \)), superior objective response rate (ORR; 42% vs 27; \( P < .01 \)), and fewer grade 3 to 4 AEs (46% vs 63%) with IO. \(^{3} \) Updated results with a 42-month minimum follow-up demonstrated persistent improvement in OS (HR, 0.66; 95% CI, 0.55-0.80; \( P < .0001 \)). The median OS in the treatment group was 47 months versus 26.6 months in the sunitinib group, with a durable response observed in a subset of patients. \(^{17} \)

Furthermore, data have shown that IO combined with a VEGF-targeted TKI has been effective. The KEYNOTE-426 trial (NCT02853331) compared pembrolizumab (Keytruda) plus axitinib (Inlyta) with sunitinib in patients with advanced RCC. The initial analysis demonstrated that at a median follow-up of 12.8 months, median OS was higher in the pembrolizumab plus axitinib group (89.9%) compared with the sunitinib group (78.3%; HR, 0.53; 95% CI, 0.38-0.74; \( P < .01 \)). The combination also showed superior PFS (HR, 0.69; 95% CI, 0.57-0.84; \( P < .01 \)) and ORR (\( P < .01 \)) compared with sunitinib. Lastly, pembrolizumab plus axitinib was shown to benefit all 3 risk groups irrespective of PD-L1 expression. \(^{18} \)

In an updated analysis of a 23-month minimum follow-up, the HR for OS in the favorable-risk group was 1.06 (95% CI, 0.60-1.86) and there was not much of a split between the groups. This is in contrast to intermediate- and poor-risk groups, where the HR for OS was 0.63 (95% CI, 0.50-0.81) and 0.69 (95% CI, 0.56-0.84) for PFS. Lastly,
the ORR was 55.8% in the combination arm versus 35% in the sunitinib arm.19
The JAVELIN Renal 101 trial (NCT02684006) compared avelumab (Bavencio) plus axitinib to sunitinib in patients with treatment-naïve, advanced clear cell RCC. The primary end points were PFS and OS. Data showed superior median PFS with avelumab plus axitinib versus 7.2 months with sunitinib, in patients with PD-L1 expression of at least 1% (HR, 0.61; 95% CI, 0.47-0.79; P < .01). Lastly, median follow-up for OS was 11.6 months for the combination group and 10.7 months for the control arm (P = .14). These studies designate a new front-line standard of care for patients with advanced RCC. For patients who have poor and intermediate disease, treatment will likely include an IO combination.

Data from the CheckMate 9ER (NCT03141177) were recently presented at the 2020 European Society for Medical Oncology Virtual Congress. In this trial, patients were randomized to receive cabozantinib (Cabometyx) plus nivolumab versus sunitinib. In the intention-to-treat arm, combination cabozantinib plus nivolumab demonstrated significantly improved PFS over sunitinib (16.6 vs 8.3 months, respectively; HR, 0.51; 95% CI, 0.41-0.64; P < .01), and a 40% decreased risk of death (median OS not reached; HR, 0.60; 95% CI, 0.40-0.89). Furthermore, the ORR was higher in patients who received cabozantinib plus nivolumab (55.7%; 95% CI, 50.1%-61.2%) compared with those receiving sunitinib (27.1%; 95% CI, 22.4%-32.3%; P < .01). Lastly, complete response rates were also higher among those receiving the combination (8.0% vs 4.6%).21 Based on these data, the FDA granted a priority review to the combination and is expected to make a decision by February 20, 2021.

It is important to caution against direct comparison across these trials. They were all conducted at different time points and significant differences exist between them in terms of primary end points, patient populations, and proportion of patients with PD-L1 expression.

There are 3 ongoing studies that will further inform the treatment landscape for patients with advanced RCC (TABLE). COSMIC-313 (NCT03937219) will evaluate the combination of nivolumab/ipilimumab/cabozantinib versus nivolumab/ipilimumab/placebo. This trial includes a control arm. CLEAR (NCT02811861) will evaluate pembrolizumab/lenvatinib (Lenvima) versus lenvatinib/everolimus (Afinitor) versus sunitinib. The primary end point is PFS. Finally, the PDIGREE Study (NCT03793166) will examine therapy escalation for patients without complete response or progressive disease following treatment with nivolumab plus ipilimumab. These patients will be randomized to continued nivolumab versus nivolumab plus cabozantinib. The outcomes of these trials may further elucidate optimal agents and sequencing for treatment.22

Investigators have also evaluated single-agent IO for the treatment of patients with metastatic RCC; specifically, pembrolizumab in the KEYNOTE-427 trial (NCT02853344). The primary end point was ORR by RECIST 1.1 criteria. The confirmed ORR for the 107 patients included in the efficacy analysis was 33.6% (95% CI, 24.8%-43.4%). The median duration of response was not reached (NR; range 1.4 + to 8.2 + months), and the median PFS was 6.9 months (95% CI, 5.1-NR). OS rates at 3 and 6 months were 97.2% and 92.4%, respectively. According to investigators, 73.6% of patients experienced AEs, 18.2% of which were greater than grade 3. Further investigation to test the additional benefit of ipilimumab to nivolumab in the frontline setting is ongoing in the CA209-8Y8 trial (NCT03873402). The trial has a primary end point of ORR and PFS and includes patients with intermediate- and poor-risk disease.23

**TABLE**

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<thead>
<tr>
<th>Study Name</th>
<th>Primary End Point</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
<th>Comparator 3</th>
<th>Comparator 4</th>
<th>Comparator 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAVELIN Renal 101</td>
<td>ORR</td>
<td>Avelumab</td>
<td>Sunitinib</td>
<td>Avelumab</td>
<td>Sunitinib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>CLEAR</td>
<td>PFS</td>
<td>Pembrolizumab</td>
<td>Lenvatinib</td>
<td>Pembrolizumab</td>
<td>Lenvatinib</td>
<td>Lenvatinib</td>
</tr>
<tr>
<td>PDIGREE</td>
<td>PFS</td>
<td>Nivolumab</td>
<td>Cabozantinib</td>
<td>Nivolumab</td>
<td>Cabozantinib</td>
<td>Cabozantinib</td>
</tr>
</tbody>
</table>

**TKI OR IO MONOTHERAPY**

The role for single-agent TKIs in the frontline space is becoming more limited as IO combinations enter the treatment landscape. However, they may still be considered in those patients with contraindications to IO or those with favorable-risk disease. The phase 2 CABOSUN trial (NCT01835158) compared frontline cabozantinib versus sunitinib for patients with intermediate- or poor-risk disease per IMDC. The primary end point of this study was PFS. Among a total of 157 patients, the median PFS was 8.6 months (95% CI, 6.8-14.0) for cabozantinib versus 5.3 months (95% CI, 3.0-8.2) with sunitinib (HR, 0.48; 95% CI, 0.31-0.74; 2-sided P < .01). Additionally, the ORR was 20.0% (95% CI, 12.0%-30.8%) versus 9% (95% CI, 3.7%-17.6%), respectively.21 When stratified by MET tumor positivity, a subanalysis of PFS data showed that cabozantinib improved PFS independent of MET status. One of the notable drawbacks of this study was that patients deemed good risk were not included. Regardless, cabozantinib is included as a treatment option for patients with good-risk disease in the National Comprehensive Cancer Network guidelines.22,24

**Safety and Toxicity**

In comparing TKI therapy to IO therapy, it is important to consider the safety profile as well as contraindications to both. The combination of nivolumab plus ipilimumab has fewer grade 3 complications compared with sunitinib, and toxicity is generally limited to the induction of ipilimumab.22 Depending on the trial, approximately 11.1% of patients required high-dose steroids to treat AEs.26 For IO-TKI therapy, patients generally experience more grade 3 complications, there is a higher toxicity profile, and the toxicity is likely to be more chronic due to the TKI component.

Several recent landmark studies have redefined our frontline treatment strategies for patients with advanced RCC. Multidisciplinary management is the future of RCC care and with combination therapy patients are living longer and better than before. However, many questions remain about optimal choice in the front line and the sequencing of therapy.22

For a full list of references, see the article at https://bit.ly/38nNs5r.

Juan Javier-DesLoges, MD, MS; Ithaaer Derweesh, MD; and Rana R. McKay, MD, are medical oncologists at UC San Diego Health in California.
WE'RE WORKING ON A BIGGER DELTA TO CHANGE THE OUTLOOK OF INDOLENT LYMPHOMA AND CLL

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MLL Fusion Proteins Emerge as a Promising Target in AML

by BRITTANY LOVELY

NOVEL AGENTS THAT DISRUPT protein-protein interactions in the MLL-menin network may be the key to unlocking new therapeutic avenues for patients with acute leukemias, which are characterized by diverse genetic and epigenetic alterations that are challenging to target, according to investigators.1

Early clinical data have demonstrated an antitumor effect of small molecule inhibitors directed at interactions of menin, a tumor suppressor protein, and MLL fusion proteins in acute myeloid leukemia (AML).2 One such agent, KO-539, is being investigated in 2 genetic subsets of AML: patients with rearrangements in KMT2A (also known as MLL1 or MLL) or with NPM1 mutations, both of which promote leukemogenesis.

KMT2A(MLL) translocations are found in approximately 5% to 10% of patients with acute leukemias, including lymphoid, myeloid, and biphenotypic subtypes.2 The 5-year survival rate for this population is approximately 35%. More than 30% of patients with AML have NPM1 mutations that, when they occur along with FLT3-ITD mutations, result in an overall survival rate of less than 50%.1

Investigators believe that menin is involved in a variety of cellular processes, including aiding in the structural modification of MLL that stabilizes the bond between MLL and lens epithelium-derived growth factor, a transcriptional coactivator believed to play a role in cancer.2 By causing a genetic disruption of the menin-MLL fusion protein interaction, they hypothesize, a novel agent could block the development of acute leukemia.1

In preclinical research, KO-539 prolonged survival compared with quizartinib, a FLT3 inhibitor, in 2 patient-derived xenograft models of NPM1/DNMT3A/FLT3-mutant AML. In a confirmatory study, animals that were NPM1- and FLT3-mutant/DNMT3A wild type and treated with quizartinib relapsed by approximately day 35; those treated with KO-539 had no evidence of disease progression after 56 days.4

Although translocations of KMT2A(MLL) occur in approximately 3% of AML cases, the mutational burden of these patients is far less than that of other cancer types; as a result, the translocations alone may result in the generation of the leukemic phenotype. Further, gene expression profiling has demonstrated overexpression of both HOXA9 and MEIS1, 2 oncogenes thought to be critical for enhanced self-renewal in AML. Specifically, transcription of the HOXA9 and MEIS1 genes depends on KMT2A(MLL)-fusion protein binding to menin. (FIGURE3)

“The menin-MLL interaction seems to trigger the upregulation of certain leukemogenic or leukemia-promoting proteins, such as HOXA9 and MEIS1,” said Amir T. Fathi, MD, in an interview with OncologyLive®. “[Developing] drugs that inhibit the leukemogenic signals can, in theory, lead to promotion of differentiation and maturation and response.” Fathi is an associate professor of medicine at Harvard Medical School and director of the leukemia program at Massachusetts General Hospital, both in Boston.

Although KMT2A(MLL) and NPM1 alterations are the current front-runners as targets for in-human studies, Fathi suggested that, in time, investigators may learn more about efficacy in other subpopulations of patients with AML whose disease may be affected by epigenetic dysregulation from the menin-MLL interaction. If so, such findings may emerge as points of interest.

“Other mutations that are seen in AML and myeloid malignancies, such as NPM1, DNMT3, EZH2, and others, appear to have their impact upstream from the menin-MLL interaction,” Fathi said. “These alterations, too, can theoretically affect the menin-KMT2A interaction and complex and promote epigenetic dysregulation and leukemogenesis.”

Study results have shown that, although NPM1 mutations are thought to initiate AML, the full leukemic phenotype requires comutations and FLT3 mutations are found in about half of cases. Overlapping patterns in gene expression profiling have been seen in mutant NPM1 that is exported to the cytoplasm (NPM1c) and KMT2A-rearranged

FIGURE. KO-539 Is a Potent and Selective Oral Inhibitor of the Menin-KMT2A (MLL) Complex

Investigators hypothesize that protein-protein interactions in the MLL-menin network have downstream implications for oncprotein activity that promotes the development of leukemia. KO-539 is designed to disrupt the interactions of menin and KMT2A (MLL).
AML. Other translocations that initiate AML, including RUNX1-RUNX1T1, CBFβ-MYH11, and PML-RARA, are also mutually exclusive with NPM1c making comutations a particular point of interest for investigators.5

Because of the potential for broad efficacy, KO-539 is being tested in a varied patient population in phase 1 of the KOMET-001 trial (NCT04067336). “We are assessing patients across a wide range of molecular subtypes to further define who may benefit from this class of targeted drug,” explained Fathi, one of the leading investigators. “We suspect that some patients with an NPM1 mutation or those with MLL rearrangements may be susceptible to response based on what we know from preclinical science, and we should study these populations carefully, but we are also assessing more broadly initially across AML to better characterize the other patient populations that may benefit.”

KO-539 ENTERS CLINICAL TESTING
KOMET-001 is the first in-human study of the menin-MLL inhibitor, which is being developed by Kura Oncology. The study will evaluate the safety and tolerability of escalating doses of KO-539 monotherapy for patients with relapsed and/or refractory AML.

“Up until now, initial studies have been done extensively in preclinical models,” Eunice S. Wang, MD, said. “If we extrapolate from some of our clinical models, we think that a dose of approximately 600 mg once per day would be effective, but because this is a first-in-human study, we [followed] the typical phase 1 study design, where we increase the dose.”

Wang serves as chief of Leukemia Service and medical director of Infusion Services at Roswell Park Comprehensive Cancer Center, as well as associate professor in the Department of Medicine at the Jacobs School of Medicine and Biomedical Sciences at the State University of New York at Buffalo.

Investigators used a novel study design and started the first dose of KO-539 at 50 mg. KO-539 was administered orally once daily to patients in 28-continuous-day cycles and, as of the August 10, 2020, data cutoff, 6 patients had proceeded through to the 200-mg dose. Following this, an expansion cohort of 3 patients at a 200-mg dose was initiated to better characterize the pharmacokinetics and exposure of KO-539.

In preliminary findings presented at the 2020 American Society of Hematology Meeting and Exposition, KO-539 demonstrated biologic activity in 6 of 8 evaluable patients in the first 4 dose cohorts of 50, 100, 200, and 400 mg.

At data cutoff on November 2, 2020, 2 patients achieved a complete remission (CR): 1 patient with SETD2/RUNXI-mutated AML in the 100-mg cohort and 1 heavily pretreated patient with a mutational profile that included NPM1, DNMT3A, and KMT2D aberrations in the 200-mg cohort. The patient who received a CR in the 100-mg cohort was dose escalated from 100 mg to 200 mg in cycle 7 and achieved a best response of CR, with measurable residual disease positivity at 100 mg, Wang said during a presentation of the data.

The remaining 4 patients—1 in the 50-mg dose cohort, 2 in the 200-mg cohort, and 1 in the 400-mg cohort—had varying mutational profiles and range of responses (TABLE). Of note, Wang highlighted that activity was seen across patients independent of concomitant CYP3A4 inhibitor therapy, which includes antifungal medicines. This may be explained by KO-539 and its metabolites acting as inhibitors and providing an advantage in overcoming drug resistance associated with CYP3A4. Investigators plan to continue evaluating KO-539 interactions with CYP3A4 inhibitors.

Although the study sample data are too small to allow for reaching conclusions, activity of the agent is promising. “The complete remission data were very exciting, for a pill taken once a day for a patient who had multiple relapses,” Fathi said. “The responding patient did not have an MLL translocation or an NPM1 mutation, but there were other alterations that may have ultimate effects on the menin-MLL interaction and the patient’s disease may thus have been susceptible to menin inhibition. It leaves open the door for the possibility of identifying other groups of patients across AML who may benefit.”

In safety data, no dose-limiting or dose-interrupting toxicities were reported. Grade 3 or higher adverse effects including pancreatitis, increased lipase, decreased neutrophil count, tumor lysis syndrome, and deep vein thrombosis were each reported in 1 patient (8.3%). Grade 1/2 AEs included nausea in 3 patients (25%), rash in 2 (16.7%), and diarrhea in 2 (16.7%).

Expansion cohorts are planned to further assess the safety and activity of KO-539 in an NPM1-mutant cohort and a KMT2A(MLL)-rearranged cohort. “Right now, the expansion cohorts are designed to target subsets of patients with AML that have those specific mutations,” Wang said. “However, if we see evidence [of efficacy] in the early dose-escalation trials, we

---

**TABLE.** Clinical Activity of KO-539 in 6 Evaluable Patients in KOMET-001 Trial

<table>
<thead>
<tr>
<th>Patient dose</th>
<th>Mutational profile</th>
<th>CYP3A4 inhibitor</th>
<th>Number of prior regimens</th>
<th>Clinical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11</td>
<td>Yes</td>
<td>3</td>
<td>Decreased peripheral blasts</td>
</tr>
<tr>
<td>200 mg</td>
<td>U2AF1, TET2, TP53, DNMT3A, PTPN11</td>
<td>No</td>
<td>4</td>
<td>Stable disease</td>
</tr>
<tr>
<td>200 mg</td>
<td>NPM1, FLI3-ITD, TET2, CUX1</td>
<td>Yes</td>
<td>4</td>
<td>Morphological leukemia-free state</td>
</tr>
<tr>
<td>200 mg</td>
<td>NPM1, DNMT3A, KMT2D</td>
<td>Yes</td>
<td>7</td>
<td>CR, MRD negativity</td>
</tr>
<tr>
<td>100 mg</td>
<td>SETD2, RUNX1</td>
<td>Yes</td>
<td>2</td>
<td>CR, MRD positivity</td>
</tr>
<tr>
<td>50 mg</td>
<td>KMT2A rearrangement</td>
<td>Yes</td>
<td>2</td>
<td>Decreasing hydrea requirement</td>
</tr>
</tbody>
</table>

CR, complete remission; MRD, minimal residual disease.
may consider trying to expand out [to other mutational subtypes], as well as to a pool of patients with leukemia that are what we call mutation agnostic.”

“There’s still a lot of ground to go and patients to enroll, but there is a lot of opportunity to probe that signal a little bit more; to learn more, and to, hopefully help these patients,” Fathi said.

OTHER MLL-TARGETING STUDIES

Another drug that aims to disrupt menin-MLL interactions is SNDX-5613, an oral inhibitor being developed by Syndax Pharmaceuticals under an FDA orphan drug designation for adult and pediatric patients with AML. The phase 1/2 AUGMENT-101 trial (NCT04065399) is testing the agent in patients with relapsed/refractory leukemias. The study, which seeks to recruit 186 pediatric and adult patients, will evaluate escalating doses of SNDX-5613 monotherapy in phase 1. After the recommended dose is established, patients will be enrolled in 1 of 3 cohorts: acute lymphoblastic leukemia or mixed phenotype acute leukemia; KMT2A(MLL)-rearranged AML; and NPM1-mutant AML.

REFERENCES


2021 GIANTS OF CANCER CARE®

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PROGRAM OVERVIEW

- Nominations are open through February 2021.
- Domestic and international nominations will be accepted.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2021 inductees.
- The 2021 Giants of Cancer Care® class will be announced in the spring of 2021.
WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDENTED SURVIVAL

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

Reduced risk of disease progression or death by 46%

Median PFS: 7.8 months (95% CI: 7.5–9.6) vs 5.6 months (95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); P < 0.00001

Extended median OS by 4.5 months

Median OS: 21.9 months (95% CI: 18.3–31.0) vs 17.4 months (95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); P = 0.0048

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.¹

NCCN RECOMMENDED

CATEGOR Y 1

Tucatinib (TUKYSA) + trastuzumab + capecitabine is the only Category 1 recommended regimen for second-line systemic treatment of HER2+ MBC by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer.¹¹²

Indication

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information

Warnings and Precautions

- Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.

*NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

†Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.²

Please see full Important Safety Information on the following pages.
In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*1

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash1

Important Safety Information

Warnings and Precautions

- Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- Embryo-Fetal Toxicity: TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysaesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.
In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

**PRIMARY ENDPOINT**

**PFS**

46% reduction in the risk of disease progression or death†

- HR = 0.54 (95% CI: 0.42-0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2-7.1) in the control arm

**EXPLORATORY ANALYSIS***

**PFS IN PATIENTS WITHOUT BRAIN METASTASES**

43% reduction in the risk of disease progression or death‡

- HR = 0.57 (95% CI: 0.41-0.80)
- Median PFS: 9.6 months (95% CI: 7.6-12.4) in the TUKYSA arm (n=211) vs 6.8 months (95% CI: 4.3-9.3) in the control arm (n=108)

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm; n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause). PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.† This exploratory analysis was not controlled for a type I error, and HER2CLIMB was not powered to test this endpoint. Results are descriptive only and are not contained in the approved product labeling.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST. The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.

- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity: avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CrCl < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.

- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see brief summary of prescribing information on adjacent pages.

**References**

TUKYSA® (tucatinib) tablets, for oral use

INDICATIONS AND USAGE

TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with advanced, unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Dosage Modifications for Adverse Reactions

The indicated TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

Hepatotoxicity (grade 2 and 3 bilirubin increase > 1.5 to 3 × ULN)

Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.

Grade 4 ALT or AST (≥ 3 × ULN)

Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.

Grade 4 ALT or AST (≥ 20 × ULN)

Permanently discontinue TUKYSA.

Other adverse reactions

Grade 3

Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.

Grade 4

Permanently discontinue TUKYSA.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>All 3 4</td>
<td>All 3 4</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade (%)</th>
<th>All 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12 0.5 9 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7 0 3 0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 0 3.6 0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 2.5 0 0.5</td>
<td></td>
</tr>
</tbody>
</table>

Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade (%)</th>
<th>All 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>13 0 15 0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>20 0.7 15 0.5</td>
<td></td>
</tr>
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</table>

Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade (%)</th>
<th>All 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>9 0.2 24 3.6</td>
<td></td>
</tr>
</tbody>
</table>

Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade (%)</th>
<th>All 3 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>25 0.5 20 0</td>
<td></td>
</tr>
</tbody>
</table>

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥ 3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE REACTIONS

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.

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade (%)</td>
<td>All 3 4</td>
<td>All 3 4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 0.5 9 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3.7 0 3 0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 0 3.6 0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 2.5 0 0.5</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>13 0 15 0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>20 0.7 15 0.5</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>9 0.2 24 3.6</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 0.5 20 0</td>
<td></td>
</tr>
</tbody>
</table>
Concomitant use of TUKYSA with a strong CYP3A inducer decreased tucatinib plasma concentrations, which may reduce the activity of TUKYSA. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: TUKYSA is used in combination with trastuzumab and capcitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk.

In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capcitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capcitabine. Refer to the Full Prescribing Information of trastuzumab and capcitabine for contraception and infertility information.

Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Infertility: Based on findings from animal studies, TUKYSA may impair male and female fertility.

Pediatric Use: The safety and effectiveness of TUKYSA in pediatric patients have not been established.

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (8%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capcitabine and trastuzumab is not recommended in patients with severe renal impairment (CrCl < 30 mL/min estimated by Cockcroft-Gault Equation), because capcitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capcitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CrCl] 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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Recent Data Drive New Strategies in Advanced Gastric, GE Cancers

by CHRISTINA T. LOGUIDICE

MANAGEMENT OF GASTRIC AND gastroesophageal (GE) malignancies has presented challenges because of significant differences in treatment efficacy based on tumor type. Specifically, the clinical distinction between esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC) has become increasingly important in stratifying patients for treatment. Further, incidence of ESCC is prevalent in Eastern Europe and Asia, whereas adenocarcinoma is most common in North America. Although these factors play a role in stratifying patients, biomarker-driven approaches, including the use of combined positive score (CPS) for PD-L1 expression, are entering the scene to define the best frontline treatment options for patients with gastrointestinal (GI) malignancies.1

At the European Society for Medical Oncology (ESMO) Congress 2020, investigators presented data for 3 practice-changing immunotherapy studies—CheckMate 649 (NCT02872116), ATTRACTION-4 (NCT02746796), and KEYNOTE-590 (NCT03189719)—offering a glimpse at the exciting progress occurring in the treatment landscape. During an OncLive Peer Exchange®, a panel of GI oncology experts discussed these studies and how the latest data are reshaping current standards of care. They also offered insights into the role biomarkers will play for patients with metastatic gastric adenocarcinoma, esophageal adenocarcinoma and ESCC, and GE junction adenocarcinoma.

CHECKMATE 649

Investigators implemented several unique study design choices for the phase 3 CheckMate 649 trial. First, unlike previous studies, the trial did not group together patients with esophageal adenocarcinoma and ESCC. Instead, those with esophageal adenocarcinomas were grouped with GE junction and stomach adenocarcinomas. “We know biologically through The Cancer Genome Atlas analysis that adenocarcinomas of the esophagus are very similar to GE junction adenocarcinomas, and they’re nothing like esophageal squamous cancer,” Yelena Y. Janjigian, MD, said. “Trials in which adenocarcinomas are grouped with squamous cell cancers should be an antiquity, and we should not be designing those studies anymore.”

Second, CheckMate 649 used a real-world chemotherapy backbone rather than cisplatin. “No one is using cisplatin and certainly not at 60 or 80 mg/m². Once again, it’s a refreshing approach and a real-world backbone therapy. Our pharmaceutical partners certainly listened while we mandated this design,” Janjigian said. “Despite previous attempts, there has not been a study that’s demonstrated that immunotherapy is helpful in the first-line setting until CheckMate 649.”

Investigators of CheckMate 649 randomly assigned 1581 patients with previously untreated, unresectable advanced or metastatic gastric cancer; GE junction cancer; or esophageal adenocarcinoma to nivolumab plus chemotherapy with capecitabine plus oxaliplatin once every 3 weeks or leucovorin, fluorouracil, and oxaliplatin (FOLFOX) once every 2 weeks; nivolumab (Opdivo) plus ipilimumab (Yervoy); or chemotherapy alone.2 Patients were enrolled regardless of PD-L1 expression; however, those with
HER2-positive status were excluded.

Data for the nivolumab plus chemotherapy arm versus chemotherapy alone arms were presented at ESMO Congress 2020; data for the nivolumab plus ipilimumab arm had not yet matured. The primary end points for the nivolumab plus ipilimumab arm had not presented at ESMO Congress 2020; data for the nivolumab plus chemotherapy alone arms were not yet matured (95% CI, 13.1-16.2) with nivolumab plus chemotherapy versus chemotherapy alone (HR, 0.71; 98.4% CI, 0.59-0.86; P < .0001). The PFS was 7.7 months (95% CI, 7.0-9.2) versus 6.1 months (95% CI, 5.6-6.9) in these cohorts, respectively (HR, 0.68; 98% CI, 0.56-0.81; P < .0001). The 12-month PFS rates were 36% and 22%, respectively.

In a subgroup analysis of patients with PD-L1 CPS 1 or higher (n = 1296), the median OS was 14.0 months (95% CI, 12.6-15.0) with nivolumab plus chemotherapy versus 11.3 months (95% CI, 10.6-12.3) with chemotherapy alone (HR, 0.77; 99% CI, 0.64-0.92; P = .0001); and for all-comers, the median OS was 13.8 months (95% CI, 12.6-14.6) versus 11.6 months (95% CI, 10.9-12.5), respectively (HR, 0.80; 99.3% CI, 0.68-0.94; P = .0002). For a CPS 5 or higher, I’m very convinced by the data that [for a patient with gastric adenocarcinoma—what you call type 2, type 3 junction of adenocarcinoma—[that the combination with nivolumab would be my preference],” Ian Chau, MD, said. He noted that the decision is more difficult for patients with tumors with a CPS between 1 and 5. “To me, when I look at CPS 1 or more—in CheckMate 649, that is 80% of the patient population, which is a large proportion of patients using that particular immuno-therapy antibody to test for PD-L1 expression—the hazard ratio is still quite impressive. If you look at the survival curves, they do clearly separate as well. I would have that discussion with the patient, to say that there is some benefit and that it has become more difficult to know whether that is going to benefit them because clearly there is a proportion of patients who don’t benefit in that lower PD-L1 expression [range],” he said.

Daniel Catenacci, MD, said that he needs more data before determining whether the combination of nivolumab and chemotherapy is a suitable option for patients with lower CPS. “Before giving my patients with a CPS of less than 1, or CPS of 1 to 5, I need to know what the actual data are for those patients, not when they are grouped with the 5-or-higher population [that might be] pulling the curve over,” he said. “Those data have not been presented. Hopefully, it’s in the publication, and if not, then I will still be asking that question.” He noted that the primary end points in CheckMate 649 were amended midtrial to be the OS and PFS outcomes specifically in the CPS 5 or higher cohort, which also led to an increase in the sample size of patients meeting these criteria. “[This end point] was clearly positive, and we will be using FOLFOX and nivolumab [for these patients],” he said, noting that whether a long-term benefit exists for those with a PD-L1 CPS of 5 or higher is an important question and one that needs clarification.

**ATTRACTION-4**

ATTRACTION-4 also evaluated nivolumab plus chemotherapy as a first-line treatment in patients with HER2-negative advanced or recurrent gastric or GE junction cancer. The study included 724 Asian patients randomly assigned 1:1 to receive nivolumab plus chemotherapy (oxaliplatin plus S-1 or capecitabine) or placebo plus chemotherapy. The primary end points were centrally assessed PFS and OS. At the interim analysis primary for PFS, which had a median follow-up of 11.6 months, the PFS was 10.45 months (95% CI, 8.44-14.75) in the nivolumab arm versus 8.34 months (95% CI, 6.97-9.40) in the placebo arm (HR, 0.68; 98.3% CI, 0.51-0.90; P = .0007), meeting the primary end point. No statistically significant difference was observed between arms in the final analysis data for OS, which had a median follow-up of 26.6 months. The median OS was 17.45 months (95% CI, 15.67-20.83) in the nivolumab plus chemotherapy arm and 17.15 months (95% CI, 15.18-19.65) in the placebo plus chemotherapy arm (HR, 0.90; 95% CI, 0.75-1.08; P = .257); however, PFS was continuously longer with nivolumab versus placebo. The overall response rate (ORR) was also higher in the nivolumab plus chemotherapy arm than in the placebo plus chemotherapy arm (57.5% vs 47.8%, respectively; P = .0088).

“Although the OS end point was not met, if you look at the data, the median OS for those patients was 17 months, but in CheckMate 649, we’re all patting one another on the back because we cleared the 1-year mark. The median OS in the experimental arm in the CPS 5 or higher category was 14 months, which is great but not as good as 17 months,” Janjigian said. Therefore, although the study did not meet the OS end point, she said the data are reassuring.

Janjigian also said that the data raise some questions. “In Japan and Korea, so many patients get I/O [immuno-oncology] in second- and third-line settings; it is approved for that. Plus, a percentage of patients go on to get second- and third-line therapy in general. Are there more patients with gastric cancer in Japan than with colon cancer in the United States? Is OS benefit even needed? Can we design trials based on PFS? We can clearly see that ATTRACTION-4 met the PFS end point,” she said.

The message from both CheckMate 649 and ATTRACTION-4 data is that immunotherapy can be used in the frontline setting. “It’s safe; it’s tolerable,” Janjigian said. No new safety signals with nivolumab plus chemotherapy were observed in data from either study. In CheckMate 649, grade 3/4 treatment-related adverse events (AEs) in those with PD-L1 CPS 5 or higher occurred in 59% of patients in the nivolumab group versus 44% in the placebo group. This was similar to the safety findings observed in ATTRACTION-4, in which grade 3 to 5 AEs occurred in 57.9% of those in the nivolumab group and 49.2% in the placebo group.

**KEYNOTE-590**

In contrast with CheckMate 649 and ATTRACTION-4, KEYNOTE-590 included
only patients with advanced esophageal cancer who could have adenocarcinoma, including Siewert type 1 esophageagastriastic junction adenocarcinoma, or ESCC.5 KEYNOTE-590 was a 1:1 randomized, international, double-blind study assessing pembrolizumab (Keytruda) plus chemotherapy (cisplatin plus 5-fluorouracil) versus chemotherapy alone in 749 patients (83% male; 73% with ESCC). Randomization was stratified by location, specifically Asia versus the rest of the world, esophageal adenocarcinoma versus ESCC, and ECOG performance status of 0 versus 1. Primary end points were OS in patients with ESCC and PD-L1 CPS 10 or higher, as well as investigator-assessed OS and PFS in 3 patient populations: all-comers with esophageal ESCC, all-comers with PD-L1 CPS 10 or higher, and the overall patient population.5

“The same tendency and efficacy were seen, not only for patients with esophageal squamous cell carcinoma but for all patients, including those with adenocarcinoma,” said Ken Kato, MD, PhD, a lead investigator on the trial. After a median follow-up of 10.8 months, the addition of pembrolizumab to chemotherapy showed superiority to chemotherapy alone in OS and PFS across tumor types evaluated (TABLE).5 In all-comers, the confirmed ORR was 45.0% in those receiving pembrolizumab versus 29.3% in those receiving chemotherapy alone. Grade 3 to 5 treatment-related AEs occurred in 72% and 68%, respectively.5

Although data from KEYNOTE-590, CheckMate 649, and ATTRACTION-4 point toward chemotherapy plus immunotherapy becoming the standard of care for patients with squamous esophageal cancer, outstanding questions exist for those with adenocarcinoma. “We’ve changed the standard of care for esophageal squamous cell carcinoma in the first-line setting, and it will be fluorouracil plus platinum with pembrolizumab. For the esophageal adenocarcinoma, that’s a little more controversial,” moderator Johanna C. Bendell, MD, said, adding that CPS 5 or higher would be the stratifying factor for these patients.

Catenacci said he agreed but explained that the threshold of CPS 10 or higher and squamous pathology are driving outcomes. “When you look at CPS less than 10, including squamous and adenocarcinoma, it’s right on the line. For me, for patients with squamous cancers that are CPS less than 10, I would select chemotherapy—folinic acid, fluorouracil, oxaliplatin—plus immuno- oncology. I would like to see the actual data before I bite at [other regimens for patients with CPS less than 10],” he said. “For adenocarcinoma, I would really like to see the data broken down in the Kaplan-Meier curves to really see the benefits there, if there are any. I suspect that those above 10 are going to be at least trending toward benefit, and I might give them the benefit of the doubt, as that would be very consistent with what CheckMate 649 is showing,” he added.

**IMPORTANCE OF BIOMARKERS**

“When we see the breakdown by expression of PD-L1 and by histology, it’s not surprising what we’re seeing in these studies. It’s exactly as would be expected,” Catenacci said. He explained that the 3 practice-changing studies collectively show the increasing importance of biomarkers in driving treatment selection for patients with gastric, GE, and GE junction cancers.

The panelists noted that in addition to PD-L1, clinicians must assess for a variety of other genomic biomarkers, including microsatellite instability (MSI) status and tumor mutational burden (TMB), as tumors with MSI-high status do not respond as well to chemotherapy, and TMB-high tumors have shown higher response rates to immune checkpoint inhibitors. “If the patient has a mismatch repair-deficient or MSI-high tumor, I do not recommend doing chemotherapy in the first-line setting,” Catenacci said.

“We’ve been successful in getting immunotherapy for these patients if they have small-volume disease. Certainly, if you’re nervous about avoiding chemotherapy in this setting, a combination of chemotherapy and immune checkpoint inhibitors could be considered, [as shown by CheckMate 649].” For assessment of patients’ tumors for biomarkers, the panelists recommended next-generation sequencing (NGS) in addition to individual testing for certain genomic alterations because NGS results can take some time to return. “You should still do HER2, PD-L1, and MSI immunohistochemistry in real time,” Janjigian said, because results from these evaluations can guide more immediate treatment decisions. Prior to the ESMO Congress 2020, HER2 testing was the only biomarker test considered absolutely essential, but with larger biomarker subsets showing increasing importance, the inclusion of NGS has been identified as a necessary tool for finding patients who may qualify for clinical trials or off-label treatments.

“Understanding all these biomarkers helps me know what the best option for first line is and over the next line of therapy and plan their sequencing over time,” Catenacci concluded.
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SATURDAY, FEBRUARY 6, 2021

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