Getting Ready for the Next Chapter in Lung Cancer

David R. Gandara, MD

PEER EXCHANGE
HEMATOLOGIC MALIGNANCIES
How MRD Guides ALL Therapy

IMMUNOTHERAPY
More PD-1/PD-L1 Drugs in Pipeline

COVID-19 IN THE CLINIC
Research-Based Section Debuts

SOCIETY OF GYNECOLOGIC ONCOLOGY
CONFERENCE HIGHLIGHTS

BREAST CANCER BRAIN METASTASES
INSIDE THE CLINIC WITH
Carey K. Anders, MD
Sarah L. Sammons, MD

CLINICAL PERSPECTIVES
GI CANCERS
Anthony B. El-Khoueiry, MD,
on New ICI Combo in HCC

DANA-FARBER CANCER INSTITUTE
Seeking a New Path for AL Amyloidosis
BY GIADA BIANCHI, MD
1L MAINTENANCE¹

Indicated for first-line maintenance treatment of advanced ovarian cancer after response to platinum-based chemotherapy.

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 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 22%, 23%, 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, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage
THE FIRST AND ONLY ONCE-DAILY ORAL PARP INHIBITOR FOR PLATINUM-RESPONSIVE ADVANCED OVARIAN CANCER

PROVEN EFFICACY IN 1L MAINTENANCE REGARDLESS OF BIOMARKER STATUS

Important Safety Information (continued)

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%).

Please see Brief Summary on the following pages.

References:

1L, first-line; PARP, poly (ADP-ribose) polymerase.

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Table 2: Dose Modifications for Non-Hematologic Adverse Reactions

- Withholding ZELUCA for a maximum of 28 days and until resolution of adverse reaction.
- Resuming ZELUCA at a reduced dose once per day.
- Discontinue medication.

Table 3: Dose Modifications for Hematologic Adverse Reactions

- For patients with platelet count <100,000/µL, platelet transfusion should be considered.
- For patients with platelet count <50,000/µL, platelet transfusion should be considered.
- Discontinue ZELUCA if neutrophil count and/or hemoglobin count have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has undergone dose reduction to 100 mg once daily.

Delirium
- ZELUCA should be discontinued.
- Discontinue ZELUCA if neutrophil count and/or hemoglobin count have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has undergone dose reduction to 100 mg once daily.

Neutrophil count <1.000/µL, or hemoglobin <8 g/dL
- Withholding ZELUCA for a maximum of 28 days, and if the neutrophil count returns to >1,500/µL, resume ZELUCA at a reduced dose per Table 1.
- Discontinue ZELUCA if there is a platelet count that is unable to return to acceptable levels within 28 days of the dose interruption period, or if the patient has undergone dose reduction to 100 mg once daily.

Hematologic adverse reaction in patients on ZELUCA.

- Withholding ZELUCA for a maximum of 28 days, and if the neutrophil count returns to >1,500/µL, resume ZELUCA at a reduced dose per Table 1.
- Discontinue ZELUCA if there is a platelet count that is unable to return to acceptable levels within 28 days of the dose interruption period, or if the patient has undergone dose reduction to 100 mg once daily.

Non-hematologic adverse reactions may be treated as follows:

- Drug discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients.
- In NOA, Grade 3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 2%, 1%, and 2% of patients.
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Values from the Table 4 study show that the most common adverse reactions were:

- Grade 3 thrombocytopenia (4%), anemia (3%), and neutropenia (2%)
- Grade 3 thrombocytopenia (3%), anemia (2%), and neutropenia (1%)
- Grade 3 thrombocytopenia (2%), anemia (1%), and neutropenia (1%)

Table 4: Adverse Drug Reactions Reported in ≥26% of All Patients Receiving ZELUCA in PRIMA

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>

**Note:** Values in parentheses indicate percentage of patients experiencing adverse reactions. ZELUCA (niraparib) is indicated for the treatment of advanced ovarian cancer in women with disease progression after two or more chemotherapy regimens and whose cancer is associated with germline germline hereditary non-polyposis colorectal cancer.
discontinuation in >2% of patients who received ZELURA included thrombocytopenia (1.50%) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%).

Table 6: 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 N=169</td>
<td>Placebo N=169</td>
</tr>
<tr>
<td>ZELURA N=169</td>
<td>Placebo N=169</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>15</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>35</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>25</td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>18</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.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of ZELURA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVARA trial. Adverse reactions in NOVARA led to dose reduction or interruption in 40% of patients, most frequently from thrombocytopenia (14%) and nausea (10%). The permanent discontinuation rate due to adverse reactions in NOVARA was 35%. The median exposure to ZELURA in these patients was 290 days.

Table 7: Abnormal Laboratory Findings in ≥25% of Patients Receiving ZELURA in NOVARA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZELURA N=367</td>
<td>Placebo N=367</td>
</tr>
<tr>
<td>ZELURA N=367</td>
<td>Placebo N=367</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>31</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</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.

Table 8: Abnormal Laboratory Findings in ≥10% of Patients Receiving ZELURA Based on Baseline Weight or Platelet Count in NOVARA

<table>
<thead>
<tr>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
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<tbody>
<tr>
<td>ZELURA N=367</td>
<td>Placebo N=367</td>
</tr>
<tr>
<td>ZELURA N=367</td>
<td>Placebo N=367</td>
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<td>Decreased hemoglobin</td>
<td>31</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</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.
Table 4: Adverse Reactions Reported in >16% of Patients Receiving ZELORA in NOVA (continued)

<table>
<thead>
<tr>
<th>Table 4: Adverse Reactions Reported in &gt;16% of Patients Receiving ZELORA in NOVA (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Disorders</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>ZELORA</strong> (437) N=463</td>
</tr>
<tr>
<td>Grades 1-4%</td>
</tr>
<tr>
<td>Grades 3-4%</td>
</tr>
<tr>
<td>Placebo (719) N=797</td>
</tr>
<tr>
<td>Placebo (719) N=797</td>
</tr>
<tr>
<td><strong>ZELORA</strong> (437) N=463</td>
</tr>
<tr>
<td>Grades 1-4%</td>
</tr>
<tr>
<td>Grades 3-4%</td>
</tr>
<tr>
<td>Placebo (719) N=797</td>
</tr>
<tr>
<td>Placebo (719) N=797</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
</tr>
<tr>
<td>85%</td>
</tr>
<tr>
<td>56%</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
</tr>
<tr>
<td>72%</td>
</tr>
<tr>
<td>21%</td>
</tr>
<tr>
<td>15%</td>
</tr>
<tr>
<td>5%</td>
</tr>
<tr>
<td>Decrease in WBC count</td>
</tr>
<tr>
<td>66%</td>
</tr>
<tr>
<td>37%</td>
</tr>
<tr>
<td>7%</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
</tr>
<tr>
<td>53%</td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td>21%</td>
</tr>
<tr>
<td>2%</td>
</tr>
<tr>
<td>Increase in AST</td>
</tr>
<tr>
<td>36%</td>
</tr>
<tr>
<td>23%</td>
</tr>
<tr>
<td>1%</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td>Increase in ALT</td>
</tr>
<tr>
<td>28%</td>
</tr>
<tr>
<td>15%</td>
</tr>
<tr>
<td>1%</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td><strong>CTCAE: Common Terminology Criteria for Adverse Events version 4.02</strong></td>
</tr>
<tr>
<td><em>Includes preferred terms of neutropenia, infection, neutropenic, fever, and febrile neutropenia.</em></td>
</tr>
</tbody>
</table>

Table 5: Abnormal Laboratory Findings in >25% of Patients Receiving ZELORA in NOVA

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
</tr>
<tr>
<td>Anemiaa</td>
</tr>
<tr>
<td>Thrombocytopeniaa</td>
</tr>
<tr>
<td>Neutropeniaa</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Infections and Infestations</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

Table 6: Adverse Reactions Reported in >16% of Patients Receiving ZELORA in GUMRA (continued)

<table>
<thead>
<tr>
<th>Table 6: Adverse Reactions Reported in &gt;16% of Patients Receiving ZELORA in GUMRA (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
</tr>
<tr>
<td>AST/ALT increased</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
</tr>
<tr>
<td>Acute kidney injury</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
</tr>
<tr>
<td>Ospnea</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Vascular Disorders</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Table 7: Abnormal Laboratory Findings in >25% of Patients Receiving ZELORA in GUMRA

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Marrow</strong></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>

Table 8: Adverse Reactions Reported in >16% of Patients Receiving ZELORA in GUMRA (continued)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Postmarketing Experience</strong></td>
</tr>
<tr>
<td><strong>Use in Specific populations</strong></td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
</tr>
<tr>
<td><strong>Risk Summary</strong></td>
</tr>
<tr>
<td>Based on its mechanism of action, ZELORA can cause feval harm when administered to pregnant women. There are no data regarding the use of ZELORA in pregnant women to inform the drug-associated risk for ZELORA. The background risk of major birth defects and miscarriage for the indicated population is unknown. In a US, general population, the estimated background risk of major birth defects is 2% to 4% and 15% to 20%, respectively. Lactation Risk Summary</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
</tr>
<tr>
<td><strong>CTCAE: Common Terminology Criteria for Adverse Events version 4.02</strong></td>
</tr>
<tr>
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</tbody>
</table>
An Expert Communicator Gets Ready for the Next Chapter in Lung Cancer

by JASON HARRIS

The rapid expansion of novel therapies and treatment strategies for patients with lung cancer represents an exciting new stage in the evolution of care in a broad range of clinical settings and tumor histologies. David R. Gandara, MD, a 2017 Giants of Cancer Care® award winner, discusses some of the major therapeutic trends in advance of the 21st Annual International Lung Cancer Congress® scheduled to take place in July.

DEPARTMENTS

ONCOLOGY & BIOTECH NEWS®
SOCIETY OF GYNECOLOGIC ONCOLOGY ANNUAL MEETING (SGO)
26 Analyses Underscore Extent of Frontline Maintenance Niraparib Benefit in Ovarian Cancer
28 Adding Trastuzumab to Chemotherapy Boosts Survival in HER2+ Uterine Serous Carcinoma

Clinical Trial in Focus
34 MIBC Trial Pairs 2 Immunotherapy Agents

Clinical Perspectives
36 Dual Checkpoint Regimen Buoy Prospects for Immunotherapy in HCC

ONCOLOGY BUSINESS MANAGEMENT

Pharmacy Operations Can Enhance Reimbursement Picture for Oncology Drugs
By Erin M. Burns, PhD, MSPH

CONTINUED ON PAGE 8
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 42.
The Future Starts to Take Shape

AS THE UNITED STATES EMERGES from the first stage of the coronavirus disease 2019 (COVID-19) pandemic, it has become increasingly clear that the oncology field will not return to its former methods of operation anytime soon—if ever.

Although the long-term impact of the pandemic is not yet clear, practicing oncologists are already grappling with a new set of challenges on logistical, financial, and clinical levels.

Consider, for example, the changes that are necessary for in-person oncology visits, as evidenced by the detailed guidance given in a recent American Society of Clinical Oncology special report. The society suggests that, in addition to following protocols for prescreening patients for COVID-19 symptoms and sanitizing facilities, practices eliminate waiting areas and create drop-off zones for those arriving by car.¹

Expenses incurred through implementing such precautions are just 1 piece of the difficult financial puzzle confronting practices. The additional costs come at a time when patient visits for nonemergency procedures have declined precipitously and, in some cases, treatment has been adjusted or postponed.

On a clinical level, our knowledge about COVID-19 and the risk the virus presents to patients with cancer continues to evolve. The research community is moving at an unprecedented speed to investigate treatment strategies and risk factors and publish their findings.

At the same time, several positive trends have emerged, most notably the lifting of outdated regulatory restrictions on telehealth visits. Although the Centers for Medicare & Medicaid Services has issued a temporary waiver on requirements for these services,² oncology leaders are hoping that these pandemic-related changes will become a permanent feature of the care landscape.

Meanwhile, we are hopeful that long-term benefits will be derived from the rapid research models being used for COVID-19. If we can fast-track this research, perhaps we can improve clinical trial designs for testing oncology therapies and shave years from development timelines.

As this crisis unfolds, our content team is dedicated to developing the best possible information that will help practicing oncologists move forward. In this issue of OncologyLive®, we are launching a new section, COVID-19 in the Clinic, focusing on the latest findings about the virus that may have an impact on oncology care. Our Oncology Business Management section features an article from one of our sister publications, Medical Economics®, about proactive steps practices can take. Our website, OncLive.com, provides up-to-the-minute expert advice and information through articles and interactive webinars.

If you have questions, concerns, or ideas to share, please reach out to our managing editor, Anita T. Shaffer, at anitashaffer@OncLive.com.

As always, thank you for reading—and stay safe.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
Hope is in bloom in RET+ NSCLC

Test for RET and other biomarkers to impact treatment plans.1,2

Identify what drives disease to help confirm your treatment course.

Targeted therapies for biomarkers like EGFR and ALK are available.3,4 Other biomarkers, like RET, represent a growing list that we’re learning more about in non–small cell lung cancer (NSCLC).5 Molecular profiling, including next-generation sequencing (NGS), can reveal which biomarkers could be driving disease.5

Treating based on targeting specific biomarkers may lead to improved patient outcomes for your NSCLC patients.2,6


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02/2020 USBP-PRP-20.005.1

Learn more about RET+ NSCLC at hopeinRET.com
THE UNCERTAINTY AND ANXIETY that the coronavirus disease 2019 (COVID-19) pandemic has brought throughout the world is simply unprecedented. This is not to suggest that the flu pandemic of 1918 or 2 world wars were not catastrophic. However, the extensive interconnectivity of nations; the rapid spread of infection; and the remarkably unfocused, uncoordinated, and often ill-conceived nature of communication has exacerbated conditions for which past experiences provide limited assistance in effectively guiding both near-term and longer-term policies.

To this complex mix we must add the rather sudden and strikingly relevant role for scientific expertise, both laboratory based and in clinical practice, in governmental efforts to control, treat, and ultimately prevent this infection. The at the same time, the scientific community is being called on to help develop rational strategies that will protect the safety of the public and simultaneously balance the impact of these measures on increasingly fragile regional and national economies.

Over the past several months, it has become almost routine in the United States to see federal and state public health officials share the podium with elected leaders at press conferences designed at least in part to help explain why certain policies are being recommended, based on the best scientific evidence available. Further, clinicians and experts in more basic aspects of laboratory science have been regularly called on to address large television and internet audiences and explain, in lay terms, current events related to COVID-19 and discuss what might transpire in the near- and longer-term future.

The message delivered today is appropriately somber but also hopeful, based on the efforts of so many working within clinical and investigative medicine and laboratory science. Clinical trials examining numerous possible treatment strategies and potential vaccine candidates serve as a counterbalance to the distressing daily reports about the number of confirmed infections and deaths from COVID-19.

The heroism of all those on the front line providing care to those seriously ill from the virus are constant reminders to the public of not only the magnificence of these individuals and clinical teams but also the shocking fragility of our health care system in its ability to adequately confront such an infectious disease.

CENSORSHIP, OVERPROMISING CAN UNDERMINE CONFIDENCE

Unfortunately, the efforts of a clinician in China to sound the alarm regarding this virus, which were not only ignored by that authoritarian government but also led to a demand that he recant his observations, highlight the often complex relationship between critically relevant science and political reality. This concern is further underscored by troubling suggestions that efforts by academics in China to report accurately on their experiences with COVID-19 are being “reviewed”...
From the Editor

(translation: censored) by governmental officials prior to submission to a peer-reviewed publication.2 There is also a worry that pronouncements from individuals who “wear the badge” of doctor might be misinterpreted as objective, valid, completely devoid of partisan politics, and accepted by the mainstream scientific community. Unfortunately, this crisis has produced bewildering examples indicating that this is a legitimate concern, including public proclamations by some doctors of unsubstantiated claims for clinical benefit associated with specific approaches to COVID-19 treatment.3

Finally, in this brief discussion of the evolving relationship between science and public policy, we must emphasize the risk of establishing unrealistic expectations and making scientifically inappropriate promises, despite the understandable desire of this community to help safely navigate these dangerous and uncharted waters.4 The concern here relates to setting realistic timelines, based on extensive past experience in similar though certainly not identical situations, for developing effective treatments and vaccines, as well as sensitive and specific COVID-19 antibody testing platforms. What will happen to the public’s faith in the scientific enterprise if unrealistic promises are not kept?

This may be a critical moment that could define for decades the relationship between clinically relevant science and the public. The future relationship will be heavily influenced by the short- and longer-term success of efforts highlighted above that, hopefully, will favorably affect individual clinical outcomes and lead to effective public health policy.

Before the introduction of COVID-19 into our lexicon, other issues challenged the long-standing support of the American public for the scientific enterprise; these matters had and will continue to have the potential to negatively influence public attitudes. Despite our focus on this viral pandemic, it is critical that these concerns be directly addressed and resolved by the scientific community. These include recent revelations of questionable and apparently secret relationships between established senior scientists in the United States and China (including members of the cancer research community)5 and the failure to publicly report the outcomes of a large percentage of completed clinical trials in a timely manner, as required by federal law.

At this moment, we should consider what it will take for the scientific community as a collective entity to self-regulate far more forcefully so that the actions of a limited number of its members do not squander the well-deserved awakening of public trust in the entire scientific enterprise.

REFERENCES
Nivolumab/Ipilimumab Combination Gains Frontline NSCLC Indication

Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) is now indicated as a frontline therapy for patients with metastatic EGFR or ALK aberrations and whose tumors express PD-L1 at a level greater than or equal to 1%, as determined by an FDA-approved test.

The approval is based on part 1 findings from the phase 3 CheckMate 227 study (NCT02477826), which showed that coadministering nivolumab and ipilimumab led to a significant survival advantage compared with chemotherapy in patients with treatment-naive disease. In a cohort of patients with PD-L1 expression that was greater than or equal to 1%, the median overall survival (OS) was 17.1 months with the doublet regimen versus 14.9 months with chemotherapy (HR, 0.79; 95% CI, 0.65-0.96; P = .007). The 1- and 2-year OS rates were 63% and 40% with the combination and 56% and 33% with chemotherapy, respectively.

In the overall population, OS data also favored the combination approach, regardless of PD-L1 expression status (17.1 vs 13.9 months; HR, 0.73; 95% CI, 0.64-0.84). The 1-year OS rates were 62% and 54% with nivolumab-ipilimumab and chemotherapy, respectively, and the 2-year OS rates also showed a benefit with the doublet therapy (40% vs 30%).

Maintenance Combination Is Approved for HRD+ Ovarian Cancer

Olaparib (Lynparza) in combination with bevacizumab (Avastin) is newly indicated as a maintenance therapy for patients with advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy with bevacizumab and whose cancer is homologous recombination deficient (HRD). The FDA also approved the myChoice CDx for use as a companion diagnostic to identify patients who would be eligible to receive the frontline therapy.

Olaparib and bevacizumab’s indication in this setting is based on findings from the pivotal phase 3 PAOLA-1 study (NCT02477644), in which the combination reduced the risk of disease progression or death by 41% compared with bevacizumab alone (HR, 0.59; 95% CI, 0.49-0.72; P < .001). After a median follow-up of 22.9 months, the median progression-free survival was 22.1 months and 16.6 months with the doublet therapy and bevacizumab, respectively.

Notably, the survival benefit was most pronounced in patients with HRD tumors, including patients with BRCA mutations (HR, 0.33; 95% CI, 0.25-0.45). In this patient subgroup, the median progression-free survival was 37.2 months with the combination and 17.7 months with bevacizumab.

Selpercatinib Gets Greenlight For RET+ NSCLC, Thyroid Cancers

Selpercatinib (LOXO-292; Retevmo) has received an accelerated approval for the treatment of patients with RET alteration–positive non–small cell lung cancer (NSCLC), medullary thyroid cancer (MTC), and other thyroid cancers. The kinase inhibitor is the first therapy approved specifically for patients whose tumors harbor RET mutations. Specifically, the indications under the approval cover adults with NSCLC that has spread; advanced MTC or MTC that has spread in patients older than 12 years who require systemic therapy; and advanced RET fusion–positive thyroid cancer in patients older than 12 years who require systemic therapy and who are radioactive iodine–refractory.

Selpercatinib’s indication is based on findings from the phase 1/2 LIBRETTO-001 trial (NCT03157128). The NSCLC cohort comprised 105 adults with RET fusion–positive NSCLC who received prior platinum-based therapy. In this group, the overall response rate was 64% (95% CI, 54%-73%). Results showed that 81% of patients responded to treatment and had a response that lasted 6 months or longer.

Among the 39 patients with treatment-naive disease, the overall response rate was 85% (95% CI, 70%-94%). Most patients (58%) responded to selpercatinib monotherapy and these responses lasted at least 6 months. Similar efficacy results were observed in LIBRETTO-001’s MTC and RET fusion–positive thyroid cancer populations, investigators said.

FDA Clears First Treatment for METex14 NSCLC

Capmatinib (Tabrecta), a highly potent and selective MET inhibitor, received an accelerated approval for patients with metastatic MET exon 14 (METex14)-mutant non–small cell lung cancer (NSCLC). The agent is the first and only therapy approved for METex14-altered NSCLC, which accounts for 3% to 4% of NSCLC diagnoses and is associated with poor prognosis.

The decision is based on primary findings from cohort 5b of the phase 2 GEOMETRY mono-1 study (NCT02414139), which showed that capmatinib monotherapy induced a 67.9% objective response rate (95% CI, 47.6%-84.1%) by independent review among 28 patients with treatment-naive disease. The disease control rate was 96.4% (95% CI, 81.7%-99.9%). In previously treated patients (n = 69), the overall response rate with capmatinib was 40.6% (95% CI, 28.9%-53.1%) and the disease control rate was 78.3% (95% CI, 66.7%-87.3%).

The FDA simultaneously approved the FoundationOne CDx assay (F1CDx) for use as a companion diagnostic for capmatinib to detect tumor mutations that lead to METex14 skipping. Capmatinib’s accelerated approval in this setting is contingent on the results of a confirmatory trial.

Subcutaneous Daratumumab Scores Approval in Multiple Myeloma

Daratumumab and hyaluronidase-fihj (Darzalex Faspro) can now be used to treat adults with newly diagnosed or relapsed/refractory multiple myeloma (MM), allowing for subcutaneous dosing of daratumumab. Of note, this indication applies to all prior approved intravenous (IV) daratumumab indications.

The decision is based on findings from the phase 3 COLUMBA (MMY3012) study (NCT03277105), in which the objective response rate was 41.1% with subcutaneous daratumumab versus 37.1% with the IV formulation, demonstrating noninferiority. Data also showed that at a median follow-up of 7.46 months, the median progression-free survival was 6.1 months with IV daratumumab compared with 5.6 months with the subcutaneous version (HR, 0.99; 95% CI, 0.78-1.26; P = .9258). The 6-month overall survival rate was 83.0% and 87.5% with the IV and subcutaneous modalities, respectively (HR, 0.90; 95% CI, 0.59-1.35; P = .6032).

COLUMBA enrolled 522 patients with relapsed/refractory MM, 259 of whom were randomized to 16 mg/kg of IV daratumumab. The remaining 263 patients received the subcutaneous version at 1800 mg, which is the recommended dose of daratumumab and should be administered in combination with 30,000 units of hyaluronidase, according to the FDA.

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Sacituzumab Govitecan Becomes First ADC Approved For TNBC

by RACHEL NAROZNIAK, MA

FOR THE FIRST TIME in the therapeutic landscape of metastatic triple-negative breast cancer (mTNBC), treatment options now include an antibody-drug conjugate (ADC). The aggressive subtype is associated with poor prognoses.

On April 22, 2020, the FDA granted an accelerated approval to sacituzumab govitecan-hziy (Trodelvy) for adults with mTNBC who have received at least 2 prior therapies for metastatic disease. The FDA’s decision was supported by efficacy data from the single-arm phase 1/2 IMM-132-01 trial (NCT01631552), which showed that sacituzumab govitecan induced durable responses in the 108 patients with mTNBC who were treated with the ADC. The overall response rate was 33.3% (95% CI, 24.6%-43.1%) and the median duration of response was 7.7 months (95% CI, 4.9-10.8).

The efficacy of sacituzumab govitecan was “much higher than what you would expect with standard chemotherapy” according to Aditya Bardia, MD, MPH, lead author of the IMM-132-01 trial. In an interview with OncologyLive®, Bardia, director of precision medicine at the Center for Breast Cancer at Massachusetts General Hospital Cancer Center in Boston, discussed how the ADC can address the unmet need seen in TNBC and the toxicities seen with the therapy.

How great was the need for a new treatment option in this breast cancer subtype?

Triple-negative breast cancer is a source of major unmet need in the field of breast oncology and in oncology in general. The risk of disease recurrence in triple-negative breast cancer is much higher compared with other breast cancer subtypes, and the prognosis of patients with this disease is also much worse than it is with other subtypes. The response rate with standard chemotherapy is in the range of 10% to 15%, and the median progression-free survival is 3 to 4 months with standard therapies in the later-line setting.

Please discuss the efficacy data that led to the approval.

Sacituzumab govitecan was tested in a basket trial with multiple cohorts, one of which included patients with metastatic triple-negative breast cancer. Early on, the team saw signs of therapeutic efficacy in patients with triple-negative breast cancer, and after discussion with the regulatory authorities, a more homogeneous patient population was enrolled. This patient population included patients with metastatic triple-negative breast cancer, and after discussion with the regulatory authorities, a more homogeneous patient population was enrolled. This patient population included patients with metastatic triple-negative breast cancer, and after discussion with the regulatory authorities, a more homogeneous patient population was enrolled. This patient population included patients with metastatic triple-negative breast cancer, and after discussion with the regulatory authorities, a more homogeneous patient population was enrolled. This patient population included patients with metastatic triple-negative breast cancer.

Moving forward, we need to investigate the efficacy of this agent in earlier lines of metastatic triple-negative breast cancer, [including the] first and second lines. We also need to look at combining this agent with other therapies like immunotherapy and PARP inhibitors, which could potentially further increase the efficacy of this agent.

This is the beginning and we need to build on this progress [by] developing better therapies and combinations to improve outcomes for our patients with triple-negative breast cancer.
FDA approval—April 22, 2020

FDA grants accelerated approval to the antibody-drug conjugate sacituzumab govitecan-hziy (Trodelvy) for adults with metastatic triple-negative breast cancer who have received at least 2 prior therapies for metastatic disease.

Mechanism of action:
- Sacituzumab govitecan combines a humanized monoclonal antibody that targets human trophoblast cell surface antigen 2 with SN-38, which is conjugated to the antibody by a cleavable linker. When delivered, SN-38 causes damage that leads to apoptosis and cell death.

How supplied:
- 180-mg lyophilized powder in a single-dose vial

Dosing:
- 10 mg/kg administered once weekly on day 1 and day 8 of a 21-day treatment cycle
  - Continue treatment until disease progression or unacceptable toxicity.
  - Do not exceed 10 mg/kg or substitute for or use with other drugs containing irinotecan or its active metabolite SN-38.

Company: Immunomedics Inc

PIVOTAL CLINICAL TRIAL

IMMU-132-01 (NCT01631552) is a multicenter, single-arm phase 1/2 trial that enrolled 108 patients with metastatic triple-negative breast cancer who received at least 2 prior treatments for metastatic disease. Patients with pretreated brain metastases who were not on high-dose steroids (>20 mg prednisone or equivalent) for at least 4 weeks were eligible. Individuals with bulky disease (mass >7 cm) or known Gilbert disease were excluded.

Efficacy population (n = 108)
- Median Age, Years (range): 55 (31-80)
- Patients Who Received Prior Chemotherapy for Metastatic Disease (%)
  - Cyclophosphamide: 18.5%
  - Platinum agents: 68.5%
  - Gemcitabine: 54.6%
  - Fluoropyrimidine agents: 51.9%
  - Eribulin: 45.4%
  - Vinorelbine: 15.7%
- Most Common Sites of Disease (%)
  - Other visceral organ*: 6.5%
  - Nonvisceral site: 23.1%
  - Liver: 41.7%
  - Lung or pleura: 56.5%
  - Visceral organ*: 76.9%

BLACK BOX WARNINGS
- Neutropenia: Severe neutropenia can occur with sacituzumab govitecan. Withhold treatment for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment and consider granulocyte colony-stimulating factor for secondary prophylaxis. Immediately initiate anti-infective therapy if febrile neutropenia occurs.
- Diarrhea: Monitor patients with diarrhea and administer fluid and electrolytes as necessary. Give atropine, if not contraindicated, for early diarrhea of any severity. Evaluate patients with late diarrhea for infectious causes at onset. If negative, initiate loperamide. In the instance of severe diarrhea, withhold treatment until diarrhea becomes grade 1 or lower; reduce subsequent doses.

OTHER WARNINGS AND PRECAUTIONS
- Hypersensitivity, nausea and vomiting, and embryo-fetal toxicity.

COMMONLY REPORTED ADVERSE EVENTS IN THE IMMU-132-01 STUDY

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sacituzumab govitecan (n=108)</th>
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<tbody>
<tr>
<td></td>
<td>All grades</td>
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<tr>
<td>Nausea</td>
<td>69%</td>
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<tr>
<td>Neutropenia</td>
<td>64%</td>
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<tr>
<td>Diarrhea</td>
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<td>Vomiting</td>
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<td>Constipation</td>
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<tr>
<td>Rash</td>
<td>31%</td>
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<tr>
<td>Decreased appetite</td>
<td>30%</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>26%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
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</tbody>
</table>

ECOG Performance Status
- 0: 28.7%
- 1: 71.3%

REFERENCES
Clinical Factors Predict Deterioration Among Patients With Cancer, COVID-19

by RACHEL NAROZNIAK, MA

AACR ABSTRACTS ADDRESS CANCER CARE IN THE AGE OF COVID-19

April 27-28, 2020

Optimal care strategies for treating patients with cancer and COVID-19 and the clinical indicators associated with poorer outcomes in this population were key inquiries of the research presented at the 2020 American Association for Cancer Research (AACR) Virtual Annual Meeting I. Preliminary findings on the efficacy of oncology agents under investigation as COVID-19 interventions and patient characteristics that correlate with higher mortality were presented as part of the program.

ECOG PERFORMANCE STATUS, cancer type, and the class of prior therapy received can predict risk for clinical worsening or death in patients with cancer who contract COVID-19, according to new findings from the Gustave Roussy Institute in Paris, France. “ECOG performance statuses of more than 1 and hematological malignancies were the [most influential] predictors of clinical worsening,” said Fabrice Barlesi, MD, PhD, general director of Gustave Roussy, during a presentation at the virtual AACR Annual Meeting. Clinical worsening was defined as the need for oxygen support for or in excess of 6 L/min, or death from any cause.¹

Data from 137 patients with cancer and COVID-19 who were treated at Gustave Roussy showed that an ECOG performance status greater than 1 was a predictor of clinical worsening in patients with the virus on both univariate (HR, 4.6; 95% CI, 2.2-10.0; P < .0001) and multivariate (HR, 3.9; 95% CI, 1.8-8.7; P = .008) analysis. Among the 136 patients with cancer and COVID-19 who were evaluated for ECOG performance status, 60% had a status of 0 to 1 and 40% had a status higher than 1. Performance status was unknown for 1 patient.

Additionally, patients with hematologic malignancies also had a higher risk for deterioration than those with solid tumors on univariate analysis (HR, 2.7; 95% CI, 1.3-5.5; P = .008). The majority (84%) of the patients treated at Gustave Roussy had solid tumors compared with 16% who were diagnosed with a blood cancer.

In contrast with ECOG performance status and disease classification, smoking status (HR, 0.8; 95% CI, 0.2-2.7; P = .72) and body mass index (HR, 1.0; 95% CI, 0.5-2.2; P = .87) “had no impact on clinical worsening,” according to Barlesi, who is also a professor of medicine at Aix-Marseille University in Marseille, France.

CLASS OF PRIOR THERAPY MAY CORRELATE WITH CLINICAL DETERIORATION

Results from a univariate analysis of individuals who received chemotherapy for their disease within the past 3 months indicated that these patients had a higher propensity for clinical worsening than those who had not been treated with chemotherapy (HR, 2.60; 95% CI, 1.32-5.13; P = .06). This trend persisted in the multivariate analysis (HR, 2.00; 95% CI, 0.96-4.22). Although prior chemotherapy correlated with a greater chance of clinical deterioration, treatment...
with immunotherapy or targeted agents in the past 3 months did not.

Of note, disease status influenced the risk for clinical deterioration for patients receiving chemotherapy. “Patients treated with cytotoxic chemotherapy are at a high risk for clinical worsening,” said Barlesi, who added that this risk specifically applied to patients with disease that is either active or metastatic, or localized or in remission.

Conversely, cytotoxic chemotherapy treatment only increased the risk of death in patients with active disease. “The risk of death remains only for patients treated with chemotherapy at an advanced stage of active disease, meaning that we may continue to treat patients with [localized disease] with cytotoxic chemotherapy in the adjuvant or neoadjuvant setting,” Barlesi said. “We have to pay attention to factors [like this] when deciding how to treat and manage patients with cancer and COVID-19.”

Most patients (59%) had active or metastatic disease. The remaining 41% of patients were in remission or had localized disease.

ECOG performance status, cancer type, and prior chemotherapy were all characteristics predictive of clinical worsening in patients with cancer and COVID-19. However, the only factor predictive of death in both univariate and multivariate analyses of overall survival was ECOG performance status greater than 1 (HR, 3.4; 95% CI, 1.2-9.8).

**COVID-19 ENGULFS GUSTAVE ROUSSY**

France’s first 3 COVID-19 cases were confirmed on January 24, 2020, 2 of which were diagnosed in Paris.7 The COVID-19 outbreak in this region “significantly affected” the Gustave Roussy Institute.

The center treated 7251 patients with cancer from March 14 to April 15, according to the conference abstract. Of those, 3616 were hospitalized. Gustave Roussy clinicians subsequently tested 1302 hospitalized patients for COVID-19 using reverse transcription polymerase chain reaction.

“Twelve percent came back positive for COVID-19,” Barlesi said. A fraction of these patients (23%) were fully asymptomatic.

After excluding 19 patients who did not have cancer, Barlesi and fellow Gustave Roussy investigators studied outcomes among the first 137 patients with cancer and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which causes COVID-19, and evaluated the treatment characteristics that contributed to clinical worsening.

Gustave Roussy’s patient outcomes “seem to be comparable to [France’s],” according to Barlesi, who noted that at the April 20 data cut-off, 20 of the 137 patients had died due to COVID-19, resulting in a mortality rate of 14.6%. On April 22, France’s mortality was 17.9% and the Paris region’s rate was 18.3%.

Clinical worsening was observed in 24.8% patients, 11% of whom were admitted to intensive care. At the time of the analysis, 16.1% of patients were still hospitalized whereas 69.3% were either discharged or receiving outpatient treatment.

Methods used to manage SARS-CoV-2 included a dual hydroxychloroquine and azithromycin regimen (HCQ/AZI); antiretroviral therapy with lopinavir in combination with ritonavir; an interleukin-6 receptor antibody; or steroids. These therapies were administered to 40, 5, 10, and 13 patients, respectively.

The absence of a standard therapeutic approach for the management of COVID-19 renders patient participation in clinical trials essential, Barlesi said. Gustave Roussy is currently recruiting patients for 8 different studies evaluating a variety of treatment interventions for COVID-19, such as the phase 2 ONCOV1D trial (NCT04342107) of HCQ/AZI in approximately 1000 French patients with advanced cancer, a positive SARS-CoV-2 test, and COVID-19 symptoms.

**REFERENCES**


**VISIT** OncLive’s COVID-19 Resource Center

onclive.com/specialty/covid-19

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**Thoracic Cancer Correlates With High COVID-19 Mortality**

**EARLY DATA FROM THE** thoracic cancers international COVID-19 collaboration (TERAVOLT), a global registry developed to collect characteristics and outcomes of patients with cancer who contract COVID-19, suggest an “unprecedentedly high” mortality among patients with thoracic malignancies, according to Marina Chiara Garassino, MD. A 34.6% death rate (n = 66/191) was observed among patients with thoracic cancers. Notably, the cause of death in the majority of these patients was attributed to COVID-19 infection—not their cancer.

The data set showed that pneumonia and pneumonitis were the most common COVID-19 complications, affecting 79.6% of patients (n = 157) with thoracic cancer. Acute respiratory distress syndrome (26.8%), multiorgan failure (7.6%), and sepsis (5.1%) were also among the complications most frequently witnessed in this patient population.

Chemotherapy administered within 3 months of a COVID-19 diagnosis increased the risk of death in this population, according to updated findings presented at the 2020 American Society of Clinical Oncology Annual Meeting.
Lung Malignancies, Bilateral Infiltrates at Diagnosis Increase Mortality Risk

CLINICAL FACTORS THAT translated to a significant increase in the risk for mortality among patients with cancer and COVID-19 include disease with lung involvement, bilateral lung infiltrates during a patient’s baseline computed tomography scan, an ECOG performance status of 2 or more, and severe neutropenia, according to findings presented by Carlos Gomez-Martin, MD, PhD, of University Hospital 12 de Octubre in Madrid, Spain.

Among the first 63 patients with COVID-19 treated in the medical oncology division of 12 de Octubre, 15 had lung cancer, 17 received a diagnosis of gastrointestinal cancer, and 10 received a diagnosis of breast cancer. Most patients (82%) had metastatic disease and 40% had lung involvement, either in the form of metastasis or primary disease.

There were 16 deaths from COVID-19 infection, 40% and 29% of which occurred in patients with lung cancer and metastatic disease, respectively. Beyond native tumor site, previous comorbidities and the use of steroids was associated with an increase in mortality. Notably, 31% of patients who were previously treated with steroids at a dose greater than 10 mg died.

Gomez-Martin noted that treatment of COVID-19 should be guided by a multidisciplinary approach, including specific antiviral therapy, supportive care, close monitoring of inflammatory parameters, and appropriate use of anticoagulants due to the risk of thromboembolic complications.

FOR MORE VISIT: onclive.com/link/7971

Adapting Melanoma Treatment, Immuno-Oncology Approaches

Delaying surgery for patients with a tumor classification below T3 is preferable and represents an opportunity to minimize disease spread in the oncology clinic in the age of COVID-19. Patients with grade T3 or greater melanoma should be given the highest surgical priority, said Paolo A. Ascierto, MD, director of the Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy at the National Tumor Institute IRCCS “Fondazione G. Pascale” in Naples, Italy. Patients requiring resection for oligometastatic disease or surgical management of complications resulting from a prior surgical procedure must also be given preference. Follow-up after surgery should be done through telemedicine and, especially when there is no evidence of disease, a clinical visit should be postponed.

In addition to outlining the best practices for postsurgical follow-up, adjuvant care, and clinical trials in melanoma, Ascierto addressed how current knowledge on immunotherapy mechanisms and managing subsequent immune-related adverse events can be extended to the treatment of COVID-19. In Ascierto’s clinic, administration of the interleukin-6 (IL-6) inhibitor tocilizumab (Actemra) emerged as a viable approach to treating respiratory distress in a patient with COVID-19, who achieved recovery 6 days after receiving tocilizumab monotherapy. Beyond anti-IL-6 agents, other classes of oncology drugs can also be used to target hyperinflammation in patients with COVID-19, such as JAK and IL-1 inhibitors.

FOR MORE VISIT: onclive.com/link/7972
Ipatasertib (GDC-0068, RG7440): An investigational, ATP-competitive AKT inhibitor²

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**Phase III • NCT04177108**

A Study of Ipatasertib in Combination With Atezolizumab and Paclitaxel as a Treatment for Participants With Locally Advanced or Metastatic Triple-Negative Breast Cancer

**Study Endpoints**

**Primary Outcome Measures:**
- PFS (investigator-assessed), defined as the time from randomization to the first occurrence of disease progression* or death from any cause
- OS, defined as the time from randomization to death from any cause

**Selected Secondary Outcome Measures:**
- ORR, defined as the proportion of patients with a CR or PR on 2 consecutive occasions ≥4 weeks apart
- DoR, defined as the time from the first occurrence of a documented objective response to disease progression* or death from any cause
- GHS/QoL scores†
- PFS, OS, ORR, and DoR in **PIK3CA/AKT1/PTEN**-altered tumors

**Selected Eligibility Criteria**
- Histologically documented TNBC that is locally advanced or metastatic and is not amenable to resection with curative intent
- Measurable disease according to RECIST v1.1
- ECOG performance status of 0 or 1
- No prior systemic therapy for inoperable LA/mTNBC
- No history of diabetes requiring insulin

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*As determined by the investigator through the use of RECIST v1.1.
†As assessed using selected questions from EORTC QLC-C30.

Information is consistent with www.ClinicalTrials.gov as of December 5, 2019.

An Expert Communicator Gets Ready for the Next Chapter in Lung Cancer

by JASON HARRIS

DAVID R. GANDARA, MD, an esteemed lung cancer specialist and 2017 Giants of Cancer Care® award winner, views himself not only as a physician-scientist, but also as an educator and communicator. He has mentored more than 50 oncologists in his career, along with PhD candidates and medical students. He also enjoys sharing his scientific knowledge with laypeople and prides himself on his ability to break down complex information for patients in language they can understand.

That’s part of the reason that Gandara regularly takes to Twitter (@drgandara) to share a mix of clinical data, medical news, and the occasional joke. “There is so much bad information on the internet, I feel like it is part of my moral obligation to do what I can to speak on a factual basis, and if there’s something that is misinformation, to point it out,” he said in an interview with OncologyLive®.

These days, Gandara, director of Thoracic Oncology and senior adviser to the director at the University of California Davis Comprehensive Cancer Center in Sacramento, intersperses informational and inspirational messages about coronavirus 2019 disease (COVID-19) in his Twitter feed.

As the public health threat from COVID-19 grew more pressing in late March, Gandara took to Twitter to ask practicing oncologists whether they would arbitrarily postpone treatment for patients with advanced NSCLC because of pandemic conditions. Of 357 respondents, 67% said they would treat patients on schedule, assuming the patient does not have an active COVID-19 infection. Approximately 20% said they would delay chemotherapy, 5% would postpone immunotherapy, and 10% would hold off on both.

“I also had a number of patients who independently responded in terms of their views, and every single one of them said, in effect, ‘I know that COVID may kill me, but lung cancer untreated will kill me.’ They said, ‘Please treat us like you are treating us in normal times.’ So although there is considerable debate about this issue, and some institutions are holding therapy, my own belief and that at our institution is we should treat patients with standards of care if we can do it safely,” Gandara said.

TAKING A THINK TANK APPROACH
Although providing care for patients with lung cancer during the pandemic will be a continuing concern, Gandara is moving forward with plans for 21st Annual International Lung Cancer Congress® (ILCC) that Physician’ Education Resource, LLC (PER®) is hosting. The meeting will be a live webcast, taking place July 23 through 25. (For information, visit GoToPER.com).

Gandara serves as one of the program directors for the meeting, along with Roy S. Herbst, MD, PhD, Ensign Professor of Medicine, professor of pharmacology, chief of medical oncology, and associate cancer center director for translational research at the Yale Cancer Center in New Haven, Connecticut, and Heather A. Wakelee, MD, professor of medicine (oncology) at Stanford University Medical Center in California. They are organizing a program
that will deliver the latest data on novel agents, clinical practice, and new developments with the potential to shape the future of lung cancer therapy. Because the conference is held shortly after the 2020 American Society for Clinical Oncology Annual Meeting in May, Gandara said attendees have the unique opportunity to hear world-renown experts interpret data.

“I’ve always referred to our meeting as a think tank, because it’s much more like that than a regular meeting,” he added. “It has not only classic lectures, but it has a number of panel discussions and case-based discussions with multidisciplinary experts, including all the disciplines that are involved in lung cancer or thoracic malignancy care.”

Gandara said many of the presentations at this year’s conference will explore newly approved agents for the treatment of lung cancer, a field that has seen rapid expansion of targeted agents and immune checkpoint inhibitor therapies during the past decade.

In the realm of targeted therapies, recent developments include FDA approvals for 2 new drugs and expanded indications for several others—all during May 2020.

On May 6, the agency authorized capmatinib (Tabrecta) for patients with non–small cell lung cancer (NSCLC) whose tumors harbor a MET exon 14 skipping mutation. Two days later, the FDA approved selpercatinib (LOXO-292; Retevmo) for patients with RET alteration–positive NSCLC, medullary thyroid cancer, and other thyroid cancers. On May 22, brigatinib (Alunbrig), which had been approved in a second-line setting, gained a frontline indication for patients with ALK–positive metastatic NSCLC.

And, on May 29, the FDA expanded the indication for ramucirumab (Cyramza), a VEGF inhibitor already approved in combination with docetaxel for progressive metastatic NSCLC, to include its use as frontline therapy in conjunction with erlotinib (Tarceva) for patients with EGFR exon 19 deletions or exon 21 L858R mutations.

These approvals follow the August 15, 2019, approval of the oral kinase inhibitor entrectinib (Rozlytrek) for adults and adolescents with solid tumors that harbor NTRK gene fusions and for adults with ROS1–mutated metastatic NSCLC.

In the immunotherapy arena, the FDA has issued multiple approvals in the past 14 months. On March 30, 2020, the agency expanded the indication for the anti–PD-L1 monoclonal antibody durvalumab (Imfinzi) in combination with chemotherapy to include first-line treatment for patients with extensive-stage small cell lung cancer (SCLC). The FDA also approved expanded SCLC indications for aytolizumab (Tecentriq), a PD-L1 inhibitor, and pembrolizumab (Keytruda), a PD-1–targeting agent, in 2019. Meanwhile, on May 15, 2020, the FDA approved the dual immunotherapy combination of nivolumab (Opdivo), an anti–PD-1 antibody, and ipilimumab (Yervoy), which targets CTLA-4, for the first-line treatment of patients with PD-L1–positive (≥1%) metastatic or recurrent NSCLC with no EGFR or ALK aberrations. In data from the phase 3 CheckMate 227 trial (NCT02477826), the combination resulted in a median overall survival (OS) of 17.1 months compared with 14.9 months with chemotherapy in patients with tumor PD-L1 expression of 1% or higher (HR, 0.79; 97.72% CI, 0.65-0.96; P = .007).

Less than 2 weeks later, the FDA approved the 2 immunotherapies in combination with 2 cycles of platinum doublet chemotherapy as a frontline treatment for patients with metastatic or recurrent NSCLC without EGFR or ALK aberrations, regardless of PD-L1 expression levels. The immunotherapy-containing regimen demonstrated a median OS of 14.1 months versus 10.7 months with chemotherapy alone (HR, 0.69; 96.71% CI, 0.57-0.86; P = .006) in the phase 3 CheckMate 9LA trial (NCT03215706).

Also in May, the FDA granted a new indication for aytolizumab as first-line therapy for patients with metastatic NSCLC with high PD-L1 expression, defined as PD-L1 staining on 50% or greater on tumor cells or 10% or greater on tumor-infiltrating immune cells. In the IMpower110 study (NCT02409342), aytolizumab demonstrated a median OS benefit of 20.2 months in the PD-L1–high population compared with 13.1 months for those who received platinum-based chemotherapy (HR, 0.59; 95% CI, 0.40-0.89; P = .0106).

“These advances are not just in one area or the other, they’re in multiple areas,” Gandara said. “Again, what that means is a practicing oncologist has to stay on top of the field, and the best way to do that is...”
Lung Cancer

BY THE NUMBERS

Lung Cancer
The Big Picture in United States

2020 estimates

New cases
228,820

Deaths
135,720

Incidence

2007 to 2016

3% PER YEAR

Mortality

2008 to 2017

51% SINCE 1990

26% SINCE 2002

5 Years of FDA Drug Approvals

2015-2020

NSCLC
4 ICIs

• Nivolumab (Opdivo)–2L monotherapy
• Pembrolizumab (Keytruda)–1L with chemotherapy; 1L monotherapy for TPS ≥1% tumors including stage III; 2L monotherapy for TPS ≥1%
• Atezolizumab (Tecentriq)–1L monotherapy for PD-L1-high tumors (TC 25% or IC ≥10%); 1L with chemotherapy for NsqNSCLC; 1L with bevacizumab (Avastin) and chemotherapy for NsqNSCLC; 2L monotherapy
• Durvalumab (Imfinzi)–Unresectable stage III NSCLC without progression after chemotherapy and RT

1 ICI Combo

• Nivolumab + ipilimumab (Yervoy)–1L for PD-L1 ≥1% tumors; 1L with chemotherapy in all PD-L1 levels

15 therapies with molecular targets

• Selrecatinib (Retevmo)–RET fusion
• Capmatinib (Tabrecta)–MET exon 14 skipping mutation
• Dacomitinib (Vizimpro)–EGFR
• Lorlatinib (Lorbruna)–ALK
• Osimertinib (Tagrisso)–EGFR
• Afatinib (Gilotrif)–EGFR
• Alectinib (Alcensa)–ALK
• Darbafenib (Tafrecta) + trametinib (Mekinist)–BRAF V600E
• Ceritinib (Zykadia)–ALK
• Brigatinib (Alunbrig)–ALK
• Ramucirumab (Cyramza) + erlotinib (Tarceva)–1L combination for EGFR-mutant tumors
• Crizotinib (Xalkori)–ROS1
• Gefitinib (Iressa)–EGFR
• Larotrectinib (Vitrakvi)–NTRK
• Entrectinib (Rozlytrek)–NTRK

LEGEND

1L, first line; 2L, second line; ES-SCLC, extended-stage small cell lung cancer; IC, tumor-infiltrating cells; ICI, immune checkpoint inhibitor; NSCLC, non–small cell lung cancer; NsqNSCLC, nonsquamous non–small cell lung cancer; RT, radiotherapy; TC, tumor cells; TPS, tumor proportion score.

REFERENCES


by CME education such as we’re providing in the ILCC.”

He is particularly excited about discussing emerging drugs that target KRAS mutations in patients with NSCLC. Leading the pack is AMG 510, a small-molecule inhibitor of KRAS G12C that is being developed under the FDA’s fast track designation for patients with previously treated metastatic disease that harbors the mutation.

Another agent that targets KRAS G12C, MRTX849, also has demonstrated promising early clinical findings. Additionally, phase 1 testing began in 2019 on a pan-KRAS inhibitor, BI 1701963 (NCT04111458), and on mRNA-5671 (V941), a KRAS vaccine (NCT03948763). Another pan-KRAS inhibitor, BBP-454, is in preclinical testing and investigators also are exploring blocking KRAS activation by targeting SOS1.

“At ILCC each year, we have a session on new drugs, new drugs that are coming out, new classes of drugs that are available. That will be one of the highlights of this meeting,” Gandara said. “In particular, although there are several drug classes where there are new findings, one that is brand new is the development of drugs for KRAS G12C mutation. KRAS—and I’ve always said this myself—has been an undruggable target because of the difficulty in developing a drug which could inhibit that mutation. But now there are drugs, and there are 5 of them in development, and we’ll be hearing about them at ILCC.”

DIAGNOSTICS DRIVE CHANGES

Gandara said care of patients with lung cancer has been advancing at a breakneck pace over the past 10 years. These changes present both challenges and opportunities for health care providers. In particular, advances in molecular testing have driven developments in the field as investigators develop better diagnostic tools.

At present, the National Comprehensive Cancer Network recommends molecular testing for patients with advanced or metastatic NSCLC for 4 oncogene-driven NSCLCs: EGFR mutations (category 1), ALK (category 1), ROSI rearrangements, and BRAF point mutations. Other molecular
targets described as emerging in the guidelines: NTRK fusions, MET amplification or exon 14 skipping mutation, RET rearrangements, and ERBB2 (HER2) mutations.\(^7\) Gandara expects KRAS G12C mutations to be added for molecular testing.

According to findings from The Cancer Genome Atlas research network, KRAS (32%) is the most common mutation in lung adenocarcinoma, the most prevalent NSCLC subtype, followed by EGFR (11%) and BRAF (7%). Each of the remaining mutations recognized in the guidelines is found in 2% or fewer tumors.\(^8\) Investigators estimate that almost 50% of patients harbor a genomic alteration that could be druggable.\(^9\)

Gandara is anticipating new data for agents targeting EGFR-mutated tyrosine kinase inhibitor (TKI)-resistant NSCLC. Although TKI therapy is well established for this population, nearly all patients with EGFR-mutated NSCLC will develop resistance to first-line therapy and overcoming that resistance is key to extending survival in these patients.\(^10\)

The third-generation TKI osimertinib (Tagrisso) was developed to overcome both EGFR sensitizing and T790M resistance mutations. The FDA approved the agent in November 2015 to treat patients with EGFR T790M mutation–positive NSCLC who progressed following previous EGFR TKI therapy. That indication was expanded in April 2018 to include frontline use for patients with NSCLC who have tumors harboring EGFR exon 19 deletions or exon 21 L858R mutations.\(^11\)

Gandara noted that investigators are also targeting RET alterations. Previous multitargeted agents may have been active against RET, but the new generation of drugs in development specifically home in on the aberration.

In addition to the newly approved selpercatinib, pralsetinib (formerly BLU-667), a selective inhibitor of RET fusions and mutations, is being developed for patients with RET-positive NSCLC under a breakthrough therapy designation. The FDA is reviewing data submitted for a new drug application based on findings for patients previously treated with platinum-based chemotherapy.\(^12\)

“So how does a practicing oncologist then test for all of these oncogenes in a time-efficient manner, with good sensitivity, good specificity, and have a turnaround time of 1 to 2 weeks, so that they can treat the patient with a personalized or precision medicine approach rather than empiric?” Gandara said. “We now have that ability—and liquid biopsy can now complement tissue next-generation sequence testing, enabling a personalized approach in even more patients.”

A PIONEERING INVESTIGATOR
Gandara has been a leader in clinical research for decades, playing key roles in the development of erlotinib (Tarceva), the first widely used EGFR TKI in the United States, and the immune checkpoint immunotherapies that have entered clinical practice since 2015. He helped set the direction of research in the field as chair of the lung committee for the Southwest Oncology Group (SWOG), a post he held for 17 years before stepping down to become a senior adviser with the research consortium in 2016.

In 2014, he played a pivotal role in developing and launching Lung-MAP, a unique public-private partnership for a master protocol incorporating molecular screening to match patients to investigational new treatments for NSCLC. Initial substudies of Lung-MAP include investigation of palbociclib (Ibrance) for patients with stage IV squamous cell lung cancer harboring cell-cycle mutations, taselisib for those with previously treated PIK3CA-positive stage IV squamous cell lung cancer, and selpercatinib for those with RET fusion-positive stage IV or recurrent NSCLC.

Gandara said his work on atezolizumab is among the major accomplishments of his career. In the phase 3 OAK trial (NCT02008227), investigators evaluated atezolizumab versus docetaxel in patients with stage IIIb or IV NSCLC who experienced progressive disease after 1 or 2 previous chemotherapy regimens, including at least 1 platinum-based regimen.\(^13\)

The group published efficacy findings in 2017 demonstrating that atezolizumab improved median OS compared with docetaxel in all patients (13.8 vs...
Liquid biopsy can now complement tissue next-generation sequencing testing.”

—DAVID R. GANDARA, MD

9.6 months; HR, 0.73; 95% CI, 0.62-0.87; \( P = .0003 \)), regardless of PD-L1 level.

Atezolizumab also improved median OS versus docetaxel among patients who expressed 1% or greater PD-L1 on tumor cells or tumor-infiltrating immune cells (15.7 vs 10.3 months, respectively; HR, 0.74; 95% CI, 0.58-0.93; \( P = .0102 \)) and among patients in the PD-L1 low or undetectable subgroup (12.6 vs 8.9 months; HR, 0.75; 95% CI, 0.59-0.96). The FDA approved atezolizumab in second-line treatment for patients with NSCLC in October 2016, based in part on data from the OAK study.

Updated results published in 2018 showed that atezolizumab had a durable effect in the initial 850 patients after a minimum follow-up of 26 months (HR, 0.75; 95% CI, 0.64-0.89; \( P = .0006 \)) and in the overall cohort after a minimum of 21 months (HR, 0.80; 95% CI, 0.70-0.92; \( P = .0012 \)).

In 2018, Gandara led a research team that conducted a retrospective analysis of the OAK data evaluating atezolizumab treatment beyond progression. Among patients who experienced progressive disease, the median post-progression OS was 8.6 versus 6.4 months in favor of the atezolizumab arm. At 18 months post progression, 26% of patients in the atezolizumab arm were still alive versus 18% in the docetaxel arm.

NEW ASSAY SHOWS PROMISE

The work Gandara is most proud of is not a drug; it is a liquid biopsy assay that he and colleagues at Foundation Medicine and Roche-Genentech developed to measure tumor mutational burden in blood (bTMB). Approximately 30% of patients have inadequate tumor tissue to perform molecular testing, and there is evidence suggesting that circulating blood-derived DNA might provide an alternative source of diagnostic material for these patients.

To validate the assay, investigators compared the results of comprehensive genomic profiling conducted on tumor tissue samples from patients who participated in the OAK study and the POPLAR trial (NCT01903993), which also involved patients with progressive NSCLC. They compared data gleaned from tumor tissue with information derived from pretreatment circulating tumor DNA in plasma from the same patients.

Investigators found that results obtained from bTMB correlated with those from tissue samples obtained via tissue and plasma. TMB greater than or equal to 16 was associated with a higher PFS benefit from atezolizumab therapy.

“We went back to [OAK] and used blood specimens that had been collected to see if we could duplicate the predictive value that had been seen with tissue analysis of TMB, and, in fact, we could,” Gandara said. “That diagnostic test has now completed its phase 3 evaluation in a trial called B-FAST (NCT03178552). We don’t know the results yet, but it is a trial randomizing to atezolizumab or platinum chemotherapy in patients with high blood TMB.”

A WRITER AT HEART

Many people who grow up to become physicians know they’re going to pursue medicine even as children. Gandara, however, wanted to be a writer. He planned to become the next Ernest Hemingway, a dream that ended abruptly after high school.

“Once I got into college, I said, ‘Oh, Journalism 101, this doesn’t interest me so much, maybe I should look at something else,’ and I decided to go into medicine,” he said. “But I have always kept my interest in writing, and I think I actually have fairly good writing skills.”

He loves putting clinical research into manuscript form and happily edits manuscripts for other investigators. Gandara is the former editor in chief of Clinical Lung Cancer and he has reviewed manuscripts for New England Journal of Medicine, Journal of the National Cancer Institute, Journal of Clinical Oncology, Oncogene, and Journal of Thoracic Oncology, among others.

“I have been able to blend my writing skills into my medical career,” he said. “I have published almost 400 peer-reviewed articles and hope to do more.”

Gandara does not restrict himself to the written word. He’ll make use of any medium available to talk about science and medicine.

The GO2 Foundation for Lung Cancer, a new organization created when the Bonnie J. Addario Lung Cancer Foundation merged with the Lung Cancer Alliance in 2019, hosts the Lung Cancer Living Room every month. The foundation invites lung cancer physicians and investigators to speak to advocates, survivors, patients, and their families about a wide range of topics including treatment options, molecular and genetic testing, clinical trials, drug discoveries, and up-to-date news about advancements.

The event is webcast around the world and Gandara makes a point to appear regularly. In a recent episode, Gandara used an analogy in which he compared the uniqueness of an individual’s fingerprint, different from all others, to the molecular “fingerprint” of their cancer as defined by next-generation sequencing.

He explained acquired resistance to targeted therapy this way: “Pretend you’re on a bus and it stops. The driver gets off and the person in the row behind him is the new driver. I say, ‘That’s what’s happening in your cancer. The back seat driver has taken over for your cancer, so we have to test to find out what it is and treat it appropriately.’”

Gandara has worked to communicate with patients and patient advocates throughout his career and finds such analogies to be an effective way to get his point across. “That’s a communication skill that I feel is very important and I try to share it when I can,” he said.
21st Annual
International Lung Cancer Congress

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Analyses Underscore Extent of Frontline Maintenance Niraparib Benefit in Ovarian Cancer

by JASON M. BRODERICK

THE SUCCESS OF FRONTLINE MAINTENANCE niraparib (Zejula) in the phase 3 PRIMA trial (ENGOT-OV26/GOG-3012; NCT02655016) extends to meeting biomarker-defined and other secondary end points and showing positive patient-reported outcomes (PROs), according to 3 analyses reported as part of the virtual platform for the Society of Gynecologic Oncology 2020 Annual Meeting on Women's Cancer (SGO 2020).1

On April 29, 2020, the FDA approved niraparib for use as a frontline maintenance treatment for women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy, regardless of biomarker status, based on findings from the PRIMA study.2

The study randomized 733 patients with stage III/IV ovarian cancer who responded to frontline platinum-based chemotherapy in a 2:1 ratio to receive maintenance niraparib (n = 487) or placebo (n = 246).1,3 Patients were randomized within 12 weeks of finishing the last cycle of chemotherapy. The study met the primary outcome measure of progression-free survival (PFS) superiority, showing that frontline maintenance with niraparib improved median PFS by 5.6 months compared with placebo.

The 3 analyses presented through the SGO 2020 platform demonstrated how this benefit was observed regardless of homologous recombination-deficient (HRD) or BRCA mutation status and was also demonstrated through several key secondary outcomes measures.

PFS BY KEY BIOMARKERS

HRD and BRCA status were key biomarkers evaluated in the trial (TABLE 1).4 Of the 733 patients randomized, 373 had tumors that were HRD; of those, 247 received niraparib and 126 received placebo. Among the 249 patients with homologous recombination-proficient tumors, 169 received niraparib and 80 received placebo. The biomarker analysis reported through the SGO platform determined that the statistically significant and clinically meaningful PFS benefit observed with niraparib in the overall population also extended to all biomarker-defined subgroups.4

Among the HRD cohort, the hazard ratio for PFS was 0.43 (95% CI, 0.310-0.588; P < .0001), and in the homologous recombination-proficient group, it was 0.68 (95% CI, 0.492-0.944; P = .0203).

In patients with BRCA mutations, the hazard ratio for PFS was 0.40 (95% CI, 0.265-0.618; P < .0001) versus 0.50 (95% CI, 0.305-0.831; P = .0064) in the BRCA wild-type population.

SECONDARY END POINTS: TFST AND PFS2

A second analysis shared through SGO showed that in the overall population, the median time to first subsequent therapy (TFST) was 18.6 months (95% CI, 15.8-24.7) with niraparib versus 12.0 months (95% CI, 10.3-13.9) with placebo (HR, 0.65; 95% CI, 0.52-0.80; P = .0001).5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall population</th>
<th>HRD, BRCA mutant</th>
<th>HRD, BRCA wild type</th>
<th>HR proficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.62 (0.502-0.755)</td>
<td>0.43 (0.310-0.588)</td>
<td>0.40 (0.265-0.618)</td>
<td>0.50 (0.305-0.831)</td>
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<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>.0064</td>
</tr>
</tbody>
</table>

HR, homologous recombination; HRD, homologous recombination-deficient; PFS, progression-free survival.
In patients with HRD tumors, the median TFST was not yet reached in patients receiving niraparib compared with 13.7 months in the placebo arm (HR, 0.46; 95% CI, 0.33-0.64; P < .0001). Among patients with homologous recombination–proficient tumors, the median TFST was 11.6 months versus 7.9 months in the niraparib (n = 169) and placebo (n = 80) arms, respectively (HR, 0.64; 95% CI, 0.46-0.90; P < .0105; Table 2).

The available results for PFS2 were at 20% data maturity in the overall population. The hazard ratio for PFS2 favored the niraparib arm in the overall (HR, 0.81; 95% CI, 0.58-1.14), HRD (HR, 0.84; 95% CI, 0.49-1.45), and homologous recombination–proficient (HR, 0.56; 95% CI, 0.34-0.91) populations.

**PATIENT-REPORTED OUTCOMES**

The third analysis shared as part of the 2020 SGO platform was a report of PROs from the PRIMA trial. 6

For the secondary end point of PROs, the investigators collected the information during the treatment period every 8 weeks for 56 weeks and then every 12 weeks thereafter. For patients discontinuing treatment, PROs were collected at the time of discontinuation, and then at 4, 8, 12, and 24 weeks (±1 week for each time point), regardless of the status of subsequent treatment.

The PRO instruments used by the investigators were FOSI, EQ-5D-5L, EORTC-QLQ-C30, and EORTC-QLQ-OV28.

The investigators determined that health-related quality-of-life scores were similar between the niraparib and control arms, based on the EORTC-QLQ-C30 and EORTC-QLQ-OV28. At each time point, the mean scores were comparable between the 2 study arms.

“Quality-of-life changes with maintenance niraparib are not significant [in PRIMA],” study investigator Dana Chase, MD, assistant professor at the University of Arizona College of Medicine – Phoenix and Creighton University at St Joseph’s Hospital and Medical Center, Arizona Oncology, The US Oncology Network, said in an interview with OncologyLive.

“With a PARP inhibitor, you have most of your adverse effects in the first couple of months on therapy. We have good data from PRIMA for the first couple of months of therapy showing that quality of life is not affected,” said Chase, adding, “What was also interesting about the data is that certain symptoms, such as fatigue, got better as patients continued their niraparib therapy...[At baseline,] the fatigue was comparable [between the niraparib and placebo arms] and then got better than placebo throughout the maintenance period.”

**EFFICACY OF NIRAPARIB**

In PRIMA’s overall population, the median PFS in the niraparib arm was 13.8 months compared with 8.2 months in the placebo group, representing a 38% reduction in the risk of progression or death with the PARP inhibitor (HR, 0.62; 95% CI, 0.50-0.76; P < .0001).

At the initiation of the study, niraparib was given at a fixed dose of 300 mg, which was adjusted to include a lower dose of 200 mg for those weighing less than 77 kg and for those with platelet counts below 150,000/μL. The median relative dose intensity in the study was 63%. Investigators noted that future presentations would focus on the potential impact of this dose change.

Patient characteristics were similar across groups. The ECOG performance status score was 1 for approximately 70% of patients, two-thirds had an International Federation of Gynecology and Obstetrics system stage of III, and a third had stage IV disease. The primary tumor locations were the ovary, fallopian tube, and peritoneum.

The majority of patients had serous histology (approximately 95%). Most patients achieved a complete response to prior chemotherapy (70%). Two-thirds of patients received neoadjuvant chemotherapy, and none received bevacizumab (Avasitn), as the study was designed before approval of the VEGF inhibitor in the frontline setting.

At the interim analysis, median overall survival was not yet reached, at just 10.8% data maturity. At this early time point, however, the 24-month overall survival rate in the full population was 84% in the niraparib group and 77% in the placebo arm (HR, 0.70; 95% CI, 0.44-1.11).

More patients experienced treatment-related adverse events (AEs) of any grade in the niraparib arm compared with placebo (96.3% vs 68.9%). Treatment-related AEs of grade 3 or higher were experienced by 63.3% of patients in the niraparib arm compared with 6.6% of those in the placebo group. The most common AEs of grade 3 severity or higher in the niraparib and placebo groups, respectively, were anemia (31.0% vs 1.6%), thrombocytopenia (28.7% vs 0.4%), platelet count decrease (13.0% vs 0%), and neutropenia (12.8% vs 1.2%).

Overall, 70.9% of patients required a dose reduction in the niraparib arm, and 12% of patients discontinued therapy due to AEs. The main AEs relating to discontinuation were myelosuppressive in nature, with 4.3% caused by thrombocytopenia.

Niraparib monotherapy is also approved as a maintenance therapy in the recurrent ovarian cancer setting; and for the treatment of patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens, and whose cancer is associated with HRD status. 7

For a full list of references, see the article at OncologyLive.com/link/7957.
Adding Trastuzumab to Chemotherapy Boosts Survival in HER2+ Uterine Serous Carcinoma

by KRISTI ROSA

The trastuzumab combination also led to increased PFS benefit in those with stage III/IV disease who were undergoing primary treatment (n = 41), with a median 17.7 months versus 9.3 months with the control regimen (HR, 0.44; 90% CI, 0.23-0.83; P = .015). Among patients with recurrent disease (n = 17), the median PFS was 9.2 months with trastuzumab versus 7.0 months with the control (HR, 0.12; 90% CI, 0.03-0.48; P = .004).

“Uterine serous carcinoma can overexpress HER2/neu growth factor receptor in 25% to 30% of cases. When we look at women with [early-stage] disease who were just treated with standard therapy, such as surgery and then chemotherapy, they can do OK; however, even in that subgroup, there are quite a few who experience recurrence, disease progression, and death,” lead study author Amanda Nickles Fader, MD, told OncologyLive® in an interview. “For women with advanced disease, that number is much higher. We have a big clinical unmet need here. We need to help these women [by finding more effective strategies to] improve their survival.”

In the investigator-initiated, randomized phase 2 study (NCT01367002), patients with primary stage/IV or recurrent, HER2/neu-positive uterine serous carcinoma were randomized 1:1 to receive intravenous carboplatin area under the curve 5 and paclitaxel at 175 mg/m² for 3 hours every 21 days for 6 cycles, with or without trastuzumab at 8 mg/kg for the first dose and 6 mg/kg in subsequent cycles, until either disease progression or unacceptable toxicity. The primary end point was PFS; a secondary end point was safety.

“The rationale [for this combination] is that trastuzumab has been well studied in combination with chemotherapy in breast cancer and other subtypes [with HER2 positivity],” said Fader, who is an associate professor of gynecology and obstetrics, vice chair of Gynecologic Surgical Operations, director of the Kelly Gynecologic Oncology Service, and director of the Center for Rare Gynecologic Cancers at Johns Hopkins Health System in Baltimore, Maryland. “We believe that trastuzumab, and monoclonal antibodies in general, work better when they’re used in concert with other therapies, including conventional cytotoxics.”

Previously published data from the study showed a median PFS of 12.6 months versus 8.0 months in the trastuzumab arm versus the control arm, respectively (HR, 0.44; 90% CI, 0.26-0.76; P = .005) and a median PFS of 17.9 months versus 9.3 months, respectively, among 41 patients with stage III/IV disease receiving primary treatment (HR, 0.40; 90% CI, 0.20-0.80; P = .013).

The rationale [for this combination] is that trastuzumab has been well studied in combination with chemotherapy in breast cancer and other subtypes [with HER2 positivity],” said Fader, who is an associate professor of gynecology and obstetrics, vice chair of Gynecologic Surgical Operations, director of the Kelly Gynecologic Oncology Service, and director of the Center for Rare Gynecologic Cancers at Johns Hopkins Health System in Baltimore, Maryland. “We believe that trastuzumab, and monoclonal antibodies in general, work better when they’re used in concert with other therapies, including conventional cytotoxics.”


table.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Carboplatin, paclitaxel, and trastuzumab</th>
<th>Carboplatin and paclitaxel</th>
<th>HR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population (N = 58)</td>
<td>12.9</td>
<td>8.0</td>
<td>0.44 (0.28-0.76; P = .005)</td>
</tr>
<tr>
<td>Median PFS, patients with stage III/IV disease undergoing primary treatment (n = 41)</td>
<td>17.7</td>
<td>9.3</td>
<td>0.44 (0.23-0.83; P = .015)</td>
</tr>
<tr>
<td>Patients with recurrent disease (n = 17)</td>
<td>9.2</td>
<td>7.0</td>
<td>0.12 (0.03-0.48; P = .004)</td>
</tr>
<tr>
<td>OS, monthsa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population (N = 58)</td>
<td>29.6</td>
<td>24.4</td>
<td>0.58 (0.34-0.99; P = .046)</td>
</tr>
<tr>
<td>Patients with stage III/IV disease undergoing primary treatment (n = 41)</td>
<td>NR</td>
<td>25.4</td>
<td>0.49 (0.25-0.97; P = .041)</td>
</tr>
</tbody>
</table>

NR, not reached; OS, overall survival; PFS, progression-free survival.

*aMedian follow-up of 25.9 months.

*bNo significant OS benefit was observed in patients with recurrent disease.
Among 17 patients with recurrent disease, the median PFS was 9.2 months versus 6.0 months with the trastuzumab regimen the control regimen, respectively (HR, 0.14; 90% CI, 0.04-0.53; P = .003).

Sixty patients were evaluable for toxicity and 57 of them were reported to have had 1 or more Common Terminology Criteria for Adverse Events (CTCAE) while receiving treatment. The most common grade 3 or higher toxicities that were reported were decreased neutrophil counts (13% with trastuzumab vs 18% with control), anemia (19% vs 7%, respectively), blood and lymphatic system disorders (16% vs 4%), and hypertension (16% vs 0%).

None of these toxicities differed significantly between arms. Although hypertension showed the largest difference (P = .055), the 5 events reported were scored by investigators as either unrelated (n = 2), unlikely (n = 2), or possibly (n = 1) treatment-related.

“The key takeaway from this study is that the updated survival analysis is promising and suggests that we should be testing all our patients with uterine serous carcinoma for HER2 [overexpression] because we now have an actionable target,” said Fader. “When we utilize trastuzumab in women with advanced disease, we know that we see improved survival outcomes, both short- and long-term.”

Investigators hope to further validate these data; however, this marks the first randomized trial to show a significant survival difference for women with uterine serous carcinoma, according to Fader, so this research offers valuable clinical insight that can still be acted upon now until further trial data are reported.

REFERENCES

Uterine serous carcinoma can overexpress HER2/neu growth factor receptor in 25% to 30% of cases.”

—AMANDA NICKLES FADER, MD

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**Indications and Usage**

Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

**Important Safety Information**

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia, and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines.
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination.
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment.
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines.
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some

<table>
<thead>
<tr>
<th>Components of Primary End Point at Week 32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Hematologic Remission at Week 32</strong></td>
</tr>
<tr>
<td><strong>Individual Components</strong></td>
</tr>
<tr>
<td><strong>Hct Control</strong></td>
</tr>
<tr>
<td><strong>≥35% Spleen Volume Reduction</strong></td>
</tr>
<tr>
<td><strong>Hct Control + Spleen Volume Reduction</strong></td>
</tr>
</tbody>
</table>

*The RESPONSE (Randomized study of Efficacy and Safety in POlycythemia vera with JAK iNhibitor ruxolitinib verSus bEst available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with polycythemia vera. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. BAT included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients enrolled in the study had an inadequate response to or are intolerant of hydroxyurea. Significantly more patients receiving Jakafi achieved the composite primary end point (≥35% spleen volume reduction and Hct control) at week 32 in the Jakafi arm maintained their response for ≥35% spleen volume reduction at week 80 in the Jakafi arm. A durability analysis was performed at week 80 in the original Jakafi arm.


Jakafi and the Jakafi logo are registered trademarks of Incyte. All other trademarks are the property of their respective owners. © 2019, Incyte Corporation. MAT-JAK-01225 07/19
Significantly more patients receiving Jakafi achieved the composite primary* and key secondary end points2,3+.

Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.

### Components of Primary End Point at Week 32

<table>
<thead>
<tr>
<th>Component</th>
<th>Jakafi (n = 110)</th>
<th>BAT (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct Control</td>
<td>23%* (n = 25)</td>
<td>&lt;1%b (n = 1)</td>
</tr>
<tr>
<td>Spleen Volume Reduction</td>
<td>60% (n = 66)</td>
<td>40% (n = 44)</td>
</tr>
<tr>
<td>Complete Hematologic Remission</td>
<td>24%*b (n = 26)</td>
<td>8%c (n = 9)</td>
</tr>
</tbody>
</table>

* The RESPONSE (Randomized study of Efficacy and Safety in P)olycthemia vera with JAK(INhibitor ruxolitinib versus bEst available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with polycythemia vera. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. BAT included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients enrolled in the study had been diagnosed with polycythemia vera for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy for Hct control, and exhibited splenomegaly. After week 32, patients were able to cross over to Jakafi treatment. A durability analysis was performed at week 80 in the original Jakafi arm.

### Durable response at week 80

- 19 of 25 patients (76%) who achieved a primary response at week 32 in the Jakafi arm maintained their response
- 51 of 66 patients (77%) who achieved Hct control at week 32 in the Jakafi arm maintained their response
- 43 of 44 patients (98%) who achieved a ≥35% spleen volume reduction at week 32 in the Jakafi arm maintained their response
- 15 of 26 patients (58%) who achieved complete hematologic remission at week 32 in the Jakafi arm maintained their response

### Durable count control

- Dose modifications may be required when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about intervening with Jakafi, visit HCP.Jakafi.com.

**References:**
1. Reference with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V2.2019, @National Comprehensive Cancer Network Inc. 2018. All rights reserved. Accessed October 29, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. 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.
2. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. 2018. All rights reserved. Accessed October 29, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. 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.
Infection

Jakafi® treatment with Jakafi. Assess lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, tuberculosis risk factors, and those at higher risk should be tested for signs and symptoms of infection and manage promptly. Infections have occurred. Delay starting therapy with Jakafi until infections are controlled. See Dosage and Administration (2.4) in Full Prescribing Information.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia. [See Warnings and Precautions (5.1) in Full Prescribing Information] • Risk of Infection [see Warnings and Precautions (5.2) in Full Prescribing Information] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [see Warnings and Precautions (5.3) in Full Prescribing Information] • Non-Melanoma Skin Cancer. [See Warnings and Precautions (5.4) in Full Prescribing Information].

Clinical Trials Experience in Myelofibrosis

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 clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 17 patients in 2 clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in 2 Phase 3 studies. In these 2 Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 x 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 x 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 6 months of treatment. Some patients double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia (see Table 2). Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, flushing and headache (see Table 1). Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in ≥ 15% of Patients in the Double-blind, Placebo-controlled Study During Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Jakafi (N=151)</th>
<th>Placebo (N=151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td>23 18 4 7 1</td>
<td>15 0 0 0 0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 10 4 3 3</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Headache</td>
<td>10 9 1 1 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>9 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7 5 2 1 0</td>
<td>5 0 0 0 0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>5 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2 0 0 0 0</td>
<td>1 0 0 0 0</td>
</tr>
</tbody>
</table>

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (N=151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70 9 4 3</td>
<td>31 0 0 0</td>
<td>100</td>
</tr>
<tr>
<td>Anemia</td>
<td>96 34 11</td>
<td>87 16 6</td>
<td>100</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 5 2</td>
<td>4 &lt;1 &lt;1</td>
<td>100</td>
</tr>
</tbody>
</table>

* Present values are worst Grade values regardless of baseline

** National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-Controlled Study • 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with Grade 3 and no Grade 4 ALT elevations. • 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. • 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations

Clinical Trial Experience in Polycythemia Vera

In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy (see Clinical Studies (14.2) in Full Prescribing Information). The most frequent adverse drug reaction was anemia. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi. Table 3 presents the most frequent nonhematologic treatment emergent adverse events occurring up to Week 32.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15 &lt;1</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>15 &lt;1</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 &lt;1</td>
<td>15 &lt;1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 0 0</td>
<td>15 0 10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 0 0</td>
<td>15 1 0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 &lt;1</td>
<td>12 &lt;1</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>9 0</td>
<td>9 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 0</td>
<td>8 0</td>
</tr>
<tr>
<td>Cough</td>
<td>8 0</td>
<td>8 0</td>
</tr>
</tbody>
</table>
selected laboratory abnormalities during treatment with Jakafi are shown in Table 6.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 &lt;1 1 &lt;1 58 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 5 &lt;1 24 3 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 0 0 &lt;1 10 &lt;1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35 0 0 8 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25 &lt;1 0 16 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated AST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25 &lt;1 0 16 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertigluricidemia</td>
<td>15 0 0 13 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence was not Grade value regardless of baseline

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 &lt;1 1 &lt;1 58 0 0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>27 5 &lt;1 24 3 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 0 0 &lt;1 10 &lt;1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>35 0 0 8 0 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25 &lt;1 0 16 &lt;1</td>
<td></td>
<td></td>
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<td></td>
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<td>25 &lt;1 0 16 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertigluricidemia</td>
<td>15 0 0 13 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prevalence was not Grade value regardless of baseline

Clinical Trial Experience in Acute Graft-Versus-Host Disease

Jakafi was studied in a multi-center, open-label, active-controlled studyup to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72 &lt;1 1 &lt;1 58 0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27 5 &lt;1 24 3 &lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 0 0 &lt;1 10 &lt;1 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Acute Graft Versus Host Disease: Nonhematological Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single-Cohort Study

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>55 41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>51 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>49 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>32 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>31 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>25 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Selected laboratory abnormalities are listed in Table 16 below

**Jakafi (N=71)**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>79 45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 40</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Jakafi is a registered trademark of Incyte. All rights reserved.

U.S. Patent Nos. 7,408,257; 8,413,626; 8,722,809; 8,822,481; 8,892,513; 9,079,919; 9,184,722; 10,016,429

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INVESTIGATORS ARE TESTING whether the addition of inhibitors targeting the PD-1 and IDO immune pathways to standard chemotherapy in the neoadjuvant setting will offer superior outcomes for patients with muscle-invasive bladder cancer (MIBC).

The phase 3 ENERGIZE trial (NCT03661320) will evaluate nivolumab (Opdivo), an anti–PD-1 agent, and linrodostat mesylate (BMS-986205), an investigational IDO inhibitor, in conjunction with standard-of-care (SOC) chemotherapy in patients with micrometastatic disease. The 3-arm trial will compare the triplet regimen with nivolumab plus chemotherapy and with chemotherapy alone in an effort to identify the optimal therapeutic approach in MIBC, where disease recurrence is common.

“The likelihood of metastatic recurrence after local treatment for muscle-invasive bladder cancer is about 50%. Many patients will have definitive local therapy, which may include removal of the bladder, but will still have metastatic recurrence and succumb to bladder cancer,” said Matthew Galsky, MD, director of genitourinary medical oncology and the Novel Therapeutics Unit at The Tisch Cancer Institute at Mount Sinai in New York, New York. “This has led to the development of therapies targeting micrometastatic cancer that might or might not be present.”

ENERGIZE seeks to enroll 1200 patients with clinical stage T2-T4a N0 or M0 MIBC. Investigators will administer gemcitabine and cisplatin to patients randomly assigned to the control arm (arm A), whereas patients randomized to 1 of the 2 experimental arms will receive nivolumab and chemotherapy alone (arm B) or combined with linrodostat mesylate (arm C; FIGURE).

After neoadjuvant therapy, all patients will undergo radical cystectomy (RC), but treatment will continue in only arms B and C. Post RC, patients in arm B will receive nivolumab monotherapy. In arm C, RC will be followed by adjuvant nivolumab and linrodostat mesylate. The coprimary end points are pathological complete response (pCR) and EFS. Secondary end points include overall survival (OS), adverse events (AEs), and serious AEs, among other outcome measures.

EARLY SIGNS OF EFFICACY

The indoleamine 2,3-dioxygenase 1 pathway has been a target of interest in MIBC for several years. In a phase 1/2 trial (NCT02658890), the combination of nivolumab plus linrodostat mesylate demonstrated efficacy with an acceptable safety profile in patients with heavily pretreated solid tumors, including participants with advanced bladder cancer.1

At a median follow-up of 24 weeks, the objective response rate (ORR) among the 27 patients with immunotherapy-naïve advanced bladder cancer was 37%. This included 3 complete and 7 partial responses. The disease control rate was 56%, leading investigators to conclude that the preliminary evidence justified further evaluation of the immunotherapy combination in bladder cancer.1

In recent years, the idea of coadministering an anti–PD-1 agent with an IDO1 inhibitor sparked “a lot of enthusiasm” in MIBC because “the response rates with the combination seemed to be higher than what was historically achieved with PD-1 or IDO1 blockade alone” in several small and uncontrolled studies, according to Galsky.

However, the excitement that initially surrounded IDO1 inhibition across disease settings swiftly waned with the release of data from the negative phase 3 KEYNOTE-252 trial/ECHO-301 (NCT02752074) of epacadostat and pembrolizumab (Keytruda), also an anti-PD-1 antibody, in patients with unresectable or metastatic melanoma. This trial enrolled 706 patients, 354 of whom received the doublet therapy; the remaining 352 were treated with pembrolizumab monotherapy. At 12 months, the OS rate was 74% in both arms. The ORR was 34.2% with the combination and 31.5% with pembrolizumab monotherapy.2

“[These data] dampened the enthusiasm for the approach and, unfortunately, had a rippling effect through clinical trials that led multiple studies that were combining IDO inhibitors with immune checkpoint blockade to be shut down or [scrapped],” Galsky said. “IDO inhibition went from

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**FIGURE. PHASE 3 ENERGIZE TRIAL (NCT03661320)**

**N = 1200**

**Eligibility criteria**
- Stage T2-T4a, N0 (<10 mm on CT or MRI) or M0 MIBC, diagnosed at TURBT and confirmed via radiographic imaging
- Variant histology is acceptable if there is a predominant urothelial component
- Eligible for RC and agrees to undergo procedure after neoadjuvant therapy
- ECOG PS of 0 or 1

**Randomization**

<table>
<thead>
<tr>
<th>Arm A: chemotherapy (gemcitabine and cisplatin)</th>
<th>Arm B: nivolumab and chemotherapy</th>
<th>Arm C: linrodostat mesylate with nivolumab and chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical cystectomy</td>
<td>No further treatment</td>
<td>Linrodostat mesylate and nivolumab</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
</tbody>
</table>

**End points**

Primary: pCR rate, EFS
Secondary: OS, AEs, SAEs, laboratory abnormalities, death, pCR, EFS

AEs, adverse events; EFS, event-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathological complete response; PS, performance status; RC, radical cystectomy; SAEs, serious adverse events; TURBT, transurethral resection of bladder tumor.
being everyone’s favorite [new] mechanism to being one that no one believed in anymore, and this was all based on 1 major phase 3 study, despite years of science suggesting that IDO1 inhibition is an important mechanism.”

SYNERGISTIC POTENTIAL
Notably, ENERGIZE is “one of the few studies trying to definitively determine whether or not there is a role for IDO inhibition in combination with immune checkpoint blockade,” according to Galsky.

Despite the negative KEYNOTE-252/ECHO-301 data, the rationale for combining an anti–PD-1 agent with an IDO inhibitor is bolstered by the synergy that can be achieved with nivolumab and linrodostat mesylate. IDO1 is an enzyme that is highly expressed in a variety of malignancies and correlates with poor prognoses due to its immunosuppressive mechanism and promotion of tumor neovascularization.3,4

“We know from multiple types of cancers, both in model systems and in the clinic, that IDO converts tryptophan to kynurenine, and the high levels of kynurenine lead to immunosuppressive effects,” Galsky said.

Kynurenine stimulates tumor regulatory T cells and suppresses effector T-cell proliferation, enabling IDO1-expressing tumors to evade the immune system.3 Linrodostat mesylate offsets this activity by decreasing kynurenine in tumor cells, restoring the functionality of immune cells such as natural killer cells, dendritic cells, and T lymphocytes while reducing the number of tumor-associated regulatory T cells.4,5

Anti–PD-1 therapies such as nivolumab have demonstrated the ability to upregulate IDO1 in multiple malignancies, supporting the use of PD-1 blockade in combination with IDO1-targeted agents.3 In MBC, tumor PD-L1 expression typically increases following treatment with cisplatin-based neoadjuvant chemotherapy. Adding a PD-1/PD-L1-directed agent to neoadjuvant chemotherapy may lead to greater control of this expression.3 Further, although IDO1 inhibitors have not demonstrated clinical activity as single agents in advanced solid tumors, preclinical models suggest that the integration of IDO1 inhibition into a chemotherapy regimen augments the anti-cancer effect.3

Testing new therapies is critical to moving the needle in MIBC because, in contrast with non-MIBC, “there has not been an improvement in the treatment of [the disease] in decades,” Galsky said. “This is 1 of a series of trials that will, hopefully, change that.”

Treatment for MIBC, which accounts for 20% to 30% of urothelial carcinoma cases, traditionally consists of neoadjuvant cisplatin-based followed by RC. Upfront RC may also be pursued, in place of chemotherapy.6

Recurrence is common among patients with MIBC, including those who undergo RC, and adjuvant cisplatin-based chemotherapy does not sufficiently extend survival in patients with recurrence.4 Chemotherapy confers a modest benefit to the 30% to 35% of patients who achieve a pCR that translates to improved survival.3 Consequently, more efficacious interventions are needed.

NEOADJUVANT IMMUNOTHERAPY
Importantly, immunotherapy has advanced the treatment paradigm in non-MIBC and is being investigated in the MIBC neoadjuvant setting, either alone or with chemotherapy, in several small studies, according to Galsky. For example, the phase 2 PANDORE trial (NCT03212651) is evaluating neoadjuvant pembrolizumab monotherapy in a maximum of 41 patients with MIBC who are not candidates for cisplatin-based chemotherapy.

The PECULIAR study (NCT03832673) has yet to begin enrollment but is designed to accrue up to 38 patients with MIBC. Participants will receive pembrolizumab and epacadostat prior to RC. The PD-L1 antibody atezolizumab (Tecentriq) is also being explored in several trials, including in combination with cabozantinib (Cabometyx) in a phase 2 study (NCT04289779).

These investigations will build on existing data that suggest a benefit with single-agent neoadjuvant immunotherapy in MIBC, said Galsky. Notably, findings from the phase 2 PURE-01 study (NCT02736266) of neoadjuvant pembrolizumab in 50 patients with MIBC showed that single-agent immune checkpoint blockade induced a pCR, defined as pT0, in 42% of patients (95% CI, 28.2%-56.8%). The percentage of patients who achieved pT0 after 3 cycles of pembrolizumab and subsequent RC was “unprecedented,” investigators said.6

Further, pT0 occurred in 54.3% of patients with a PD-L1 combined positive score greater than or equal to 10% versus 13.3% of patients with a score less than 10%, leading investigators to conclude that neoadjuvant pembrolizumab might be most advantageous in patients who are PD-L1-positive or who have a high tumor mutation burden, given that the top scores of pre-therapy burden were associated with pT0.6

The viability of single-agent neoadjuvant immune checkpoint blockade in MIBC is also supported by results from the phase 2 ABACUS trial (NCT02662309), which evaluated 2 cycles of atezolizumab prior to RC in 95 patients. The study met its primary end point with a pCR of 31% (95% CI, 21-41). Importantly, no new safety signals were identified with neoadjuvant atezolizumab, which did not complicate RC.7

In contrast with PURE-01, PD-L1 expression did not correlate with outcome (P >.05). However, high presence of intraepithelial CD8-positive cells was associated with immunotherapeutic response: the pCR was 40% (95% CI, 26%-57%) in patients with these cells versus 20% (95% CI, 9%-35%) in participants without them (P <.05), and the 1-year relapse-free survival rate was 85% (95% CI, 67%-94%) in the CD8-positive population.7

With a different trial design, ENERGIZE will answer a clinical question that could have actionable impact: Does dual anti–PD-1 and IDO1 inhibition have a role in the MIBC treatment landscape?

Although many clinical trials have suspended enrollment due to health concerns related to the coronavirus disease 2019 pandemic, ENERGIZE remains open for enrollment and continues to accrue patients across many of its approximately 180 locations worldwide, including sites in the United States.
Dual Checkpoint Regimen Buoy Prospects for Immunotherapy in HCC

by RACHEL NAROZNIAK, MA

ARRIVING AFTER SEVERAL negative phase 3 trials testing single-agent immune checkpoint inhibitors (ICIs), the recent approval of nivolumab (Opdivo) in combination with ipilimumab (Yervoy) demonstrates the utility of dual immunotherapy for patients with hepatocellular carcinoma (HCC).

“This [approval] solidifies the role of immunotherapy-based combinations in the field,” said Anthony B. El-Khoueiry, MD, lead author of the CheckMate 040 study (NCT01658878) that led to doublet’s approval on March 10, 2020, for patients with HCC who received prior sorafenib (Nexavar) therapy. “We have seen single-agent PD-1 antibodies like pembrolizumab [Keytruda] and nivolumab show activity in small phase 1 and phase 2 studies and [subsequently] receive accelerated approvals, but when it came to phase 3 studies, these agents did not meet primary end points with statistical significance.”

Motivated by the hypothesis that concurrently administering more than 1 ICI could lead to greater anticancer activity than single-agent immune checkpoint blockade, investigators planned and subsequently initiated several studies to test this proposed synergy. CheckMate 040 was among these clinical efforts and evaluated the efficacy of nivolumab and ipilimumab, a CTLA-4 inhibitor, in cohort 4 (n = 49). Patients received the ICIs at 1 mg/kg and 3 mg/kg, respectively, every 3 weeks for 4 cycles, followed by 240 mg of nivolumab every 2 weeks until disease progression or unacceptable toxicity.1

The overall response rate (ORR) was 33% (95% CI, 20%-48%), with 4 complete responses (CRs) and 12 partial responses (PRs). The duration of response with the immunotherapy doublet ranged from 4.6 months to more than 30.5 months and 31% of responses lasted at least 24 months, outperforming nivolumab monotherapy, which was assessed in cohorts 1 and 2 (TABLE).1

“When we look at the efficacy data from cohort 4, the results are really quite striking. There was a complete response rate of 8%. These patients not only responded to the combination [but also had] complete responses that were quite durable,” said El-Khoueiry. “[These results] build on the single-agent activity that’s been seen [and affirm] that immunotherapy-based combinations may potentially show very promising activity.”

ICI MONOTHERAPY APPROVALS

The FDA cleared nivolumab monotherapy for use in this setting in September 2017 based on efficacy data from a subset of 154 patients with HCC from cohorts 1 and 2 of CheckMate 040 who either progressed on sorafenib or were unable to tolerate the tyrosine kinase inhibitor. Patients received nivolumab at 3 mg/kg every 2 weeks. Findings indicated that treatment with the ICI induced a 14% ORR, with a 2% CR rate and a 12% PR rate by blinded independent central review per RECIST 1.1 criteria.1

In November 2018, single-agent pembrolizumab gained approval for patients with HCC who have been treated with sorafenib based on results from the KEYNOTE-224 trial (NCT02702414). Participants in the single-arm study received pembrolizumab intravenously at 200 mg every 3 weeks. Pembrolizumab demonstrated a 17% ORR among 104 patients, including a 1% CR rate and a 16% PR rate by blinded independent review per RECIST 1.1 criteria.2

THE SEARCH FOR ACTIVITY IN THE FRONT LINE

Building upon the efficacy of single-agent ICI therapy in HCC has proved challenging. Data from the phase 3 CheckMate 459 trial (NCT02576509) of frontline nivolumab versus standard-of-care (SOC) sorafenib in 1009 patients with unresectable HCC, did not meet statistical significance for improved overall survival (OS; HR, 0.85; 95% CI, 0.72-1.02; P = .0752). Although CheckMate 459 missed its primary end point of OS, findings trended toward an OS benefit with the PD-1 inhibitor.3

Meanwhile, pembrolizumab monotherapy fell short of reaching a prespecified benchmark for statistical significance compared with placebo as second-line therapy for patients who previously received sorafenib, according to findings from the phase 3 KEYNOTE-240 trial (NCT02702401). The study enrolled 413 patients who were randomized to receive best supportive care plus either pembrolizumab or placebo. The OS for pembrolizumab therapy had an HR of 0.78 (95% CI, 0.611-0.998; P = .0238).4

The lackluster performance of ICI monotherapies in phase 3 investigations has since prompted an interest in immunotherapeutic combinations: “It was important to build on [these] data by [conducting] studies of combination therapies,” said El-Khoueiry, chair of

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TABLE. Efficacy Data from the CheckMate 040 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab and ipilimumab (cohort 4; n = 49)*</th>
<th>Nivolumab (cohorts 1 and 2; n = 154)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed overall response rate (95% CI)</td>
<td>33.0% (20%-48%)</td>
<td>14% (9%-21%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Partial response</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Duration of response, range in months</td>
<td>4.6-30.5+</td>
<td>3.2-51.1+</td>
</tr>
</tbody>
</table>

*Results are based on a minimum follow-up of 28 months.

**Results are based on a minimum follow-up of approximately 27 months. Patients received nivolumab at 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity.
Clinical Perspectives

GASTROINTESTINAL CANCERS

The dual ICI approach is among a number of immunotherapeutic combinations under investigation as first-line treatment of HCC, particularly those that pair an ICI with VEGF inhibition.

On May 29, 2020, the FDA approved the combination of atezolizumab (Tecentriq), a PD-L1 inhibitor, with bevacizumab (Avastin), a VEGF inhibitor, for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.5

The decision was based on findings from the phase 3 IMbrave150 study (NCT03434379), in which the combination was compared with sorafenib as frontline therapy for 501 patients.

At a median follow-up of 8.6 months, the median progression-free survival was 6.8 months with atezolizumab and bevacizumab versus 4.3 months with sorafenib. The median OS was not estimable among the 336 patients evaluable in the combination arm and 13.2 months in the sorafenib group (n = 165; HR, 0.58; 95% CI, 0.42-0.79; P < .001).6

“There was a 42% reduction in the risk of death with atezolizumab and bevacizumab,” El-Khoueiry said. The approval of the regimen, he noted, “would move the immunotherapy-based combination approach to the frontline setting.”

Updated IMbrave150 results, presented at the 2020 Gastrointestinal Cancers Symposium, showed that the median time to deterioration (TTD) was better among patients who were treated with the doublet therapy compared with patients who received sorafenib. The median TTD was 11.2 months with the combination versus 3.6 months with sorafenib (HR, 0.63).

This advantage extended to the TTD of physical functioning (median TTD, 13.1 vs 4.9 months; HR, 0.53; 95% CI, 0.39-0.73) and role functioning, which favored atezolizumab and bevacizumab (9.1 vs 3.6 months; HR, 0.62; 95% CI, 0.39-0.73). The dual immunotherapy approach also delayed the TTD in patient-reported loss of appetite, fatigue, pain, and diarrhea.7

Other activity in the field includes regimens that combine PD-1/PD-L1 inhibition with multikinase inhibitors, El-Khoueiry said. The combination of pembrolizumab with lenvatinib, which inhibits VEGF and other kinases implicated in pathologic angiogenesis, is being explored in the phase 3 MK-7902-002/E7080-G000-311/LEAP-002 study (NCT03713593). The trial will compare the doublet with single-agent lenvatinib in an estimated 750 patients with advanced HCC.

In July 2019, the FDA granted the combination a breakthrough therapy designation for patients with newly diagnosed, advanced, and unresectable HCC that is not amenable to locoregional treatment. The classification was based on positive interim findings from the single-arm, phase 1b KEYNOTE-524/Study 116 (NCT03006926) of pembrolizumab and lenvatinib in 104 patients with HCC.8

Additionally, the combination of atezolizumab and cabozantinib (Cabometyx), which inhibits VEGF and other kinases, is under evaluation versus sorafenib in the phase 3 COSMIC-312 study (NCT03755791).

Investigators are seeking to recruit 740 patients with advanced disease who have not received prior systemic therapy. Patients who are not randomized to the doublet regimen or sorafenib will receive cabozantinib monotherapy. Investigators will interpret the data from this arm to compare the efficacy of single-agent cabozantinib with sorafenib.

The phase 3 HIMALAYA trial (NCT03298451) is evaluating the efficacy of combining durvalumab (Imfinzi), which also targets PD-L1, and tremelimumab, which is directed at CTLA-4, in patients with unresectable, advanced HCC who have not previously received systemic treatment and are ineligible for locoregional therapy versus sorafenib. The study is also testing single-agent durvalumab in this patient population.

In January 2020, the FDA granted orphan drug status to the combination.9

QUESTIONS REMAIN

As HCC specialists spearhead studies designed to answer the question of whether or not immunotherapeutic combinations are a key to unlocking greater efficacy in HCC, strategies for optimal sequencing remain elusive due to the highly active nature of these investigations.10

“There are a lot of questions about how to best sequence these agents because of the shifting data in the field,” El-Khoueiry said.

He noted that if the combination of atezolizumab and bevacizumab becomes the dominant regimen in the first-line setting, “there are very little data on what to use after [this regimen] and how to sequence the agents. This is a challenge in the field, and we need to generate more data, whether from clinical trials or real-world evidence.”

For a full list of references, see the article at OncLive.com.
Pharmacy Operations Can Enhance Reimbursement Picture for Oncology Drugs

by ERIN M. BURNS, PHD, MSPH

PHARMACISTS CAN PLAY A ROLE in the drug reimbursement process for oncology products, which are among the most expensive of all pharmaceuticals. Pharmacy leaders who spoke with OncologyLive\textsuperscript{a} said they can assist with revenue cycle management process, working with the billing and finance teams if any payment is denied and ensuring therapies have prior authorization from private payers.

Reimbursement for drugs has historically been determined with the average wholesale price, which was set by manufacturers. But the average annual cost of new cancer drugs continues to trend upward, although the median cost dropped by $13,000 in 2018 to $149,000, and the cost per product ranged between $90,000 and over $300,000 (FIGURE).\textsuperscript{1}

As the net cost of cancer drugs is anticipated to continue to increase, policy has been set such that costs are determined using the average selling price (ASP), which is calculated by dividing the manufacturer’s total revenue for a particular drug by the number of units sold (excluding particular sales, including those to the government).

For Medicare Part B drugs, the Centers for Medicare & Medicaid Services reimburses based on the ASP + 6% (4.3% due to sequestration),\textsuperscript{2} and there is also a difference if an infusion center is a hospital-based outpatient department. In this case, the Outpatient Prospective Payment System bundles drugs that cost less than a predetermined threshold. Private insurance generally reimburses a negotiated percentage of the charges.

“Information such as site of care and the payer mix play a particularly significant role [in determining reimbursement],” explained Scott A. Soefje, PharmD, MBA, director of Pharmacy Cancer Care Services at the Mayo Clinic in Rochester, Minnesota.

Often institutions will implement a charge master, which lists individual costs for each drug. The role of the pharmacy in this process varies by institution. Drug markups are determined by institutions, with a recent report of a median of 2.4 (range, 1.8-3.0) for cancer drugs.\textsuperscript{3} In this study, a markup ratio of 3.5 means that for every $100 that Medicare pays, the hospital charged $350, or $250 in excess charges. This report also found higher markups for medical oncology services were associated with for-profit status.

Institutions must determine which price to use as the baseline value for the markup among average wholesale price, ASP, wholesale acquisition cost, and actual acquisition cost. Although pharmacy operations may have input on this process, it may be determined based on what can easily be integrated with the electronic health record and billing system to generate charges.

“The final area that pharmacy can affect is the cost of the drug,” Soefje explained. “Through contracting, the department can negotiate discounted prices. If the charges are set on something other than acquisition cost, then the difference between the charge and cost widen and revenue increases. Those institutions that choose to use acquisition cost feel it is important to pass on the savings from negotiations to the customer.”

Community practices have benefited by having pharmacists on staff. They can help manage drug inventory, ensure safe prescribing practices, keep up with current guidelines, improve outcomes, educate patients, and assist the billing department to ensure reimbursement.\textsuperscript{4-6}

According to Ryan Haumschild, PharmD, MS, MBA, director of Pharmacy Services at Emory Healthcare in Atlanta, Georgia, working with payers can be difficult due to the preferred formulary and preferred products, particularly when trying to provide optimal care for patients.

*Initially, a prescriber may choose a medication that he or she feels is most appropriate for the patient, but due to payer restrictions and preferred products, oftentimes it requires a lot of additional communication and coordination to make sure that we’re dispensing the right product for the patient when they show up,” Haumschild said. “It requires a lot more...
coordination and operational burden, and it requires us to have multiple sites and carry multiple products based on payer preferences.”

Specifically, challenges arise with patients who have cancer because providers want to treat them as soon as possible. Delays in preauthorizations from the payer can make the process more complex in that pharmacists must ensure that the operations of switching out drugs occur safely and that the dosing and frequency are considered at the time the patient needs to be treated.

Other challenges arise after reviewing denied claims when no preauthorizations are required. Haumschild also emphasized the importance of building in feedback from high-cost drugs to be sure enough information is supplied to help ensure reimbursement.

THE PHARMACIST’S ROLE
According to Haumschild, pharmacists can aid prescribers with therapy choices to ensure that drugs are FDA approved, included in the National Comprehensive Cancer Network guidelines, and will be reimbursed. Pharmacists also help with drug information in the electronic health records. Pharmacists who are having the medications compounded and dispensed must choose the correct medications, the correct National Drug Code, and ensure the charge is captured appropriately when it is administered.

According to Soefje, a drug is not likely to be reimbursed if it is not in the compendia at the required level for the use proposed. In this case, the pharmacy can help with patient assistance programs to try to obtain the drug.

“Once a denial has occurred, pharmacy help to ensure all the appropriate coding has been done to ensure the claim is accurate,” Soefje said. “Often, a pharmacist can help clarify the coding or knows something about the patient that the coders missed that help the claim. Pharmacists are also involved when the denial is going to appeal and requires a letter of medical necessity and/or literature support.”

THE FUTURE OF DRUG REIMBURSEMENT
“I see a lot of changes coming,” Haumschild explained. “As we see less revenue coming in based on hospital-based reimbursement, we’ve got to figure out another way to still be able to provide care. With reimbursement shifts in site of care, it also takes the care away from the hospital or the clinic, which creates additional strategies on how to ensure our patients are getting the best treatment possible.”

Haumschild also noted that more drugs will migrate into the ambulatory care and outpatient setting and more scrutiny over drug expenses may potentially reduce the amount of reimbursement.

According to Soefje, the biggest shift will be toward value-based payments where reimbursement will be tied to episodes of care and the outpatient focus will shift from revenue to cost. “The goal of the pharmacy will be to minimize cost while maximizing value,” Soefje explained. “The institution will receive bonus payments for high-quality care, and the focus will shift to outcomes and patient experiences. In the next 3 to 5 years, more than half of all payments will be in some form of value-based payments.”

Soefje also explained that institutions must shift to consider the total cost of care rather than individual drug costs, and the costs of drugs will be evaluated based on the associated patient outcomes. “The cheapest drug may not always be the best and we must always remember that the drug that does not work or is not taken is the most expensive drug,” Soefje said.

TIPS FOR MOVING FORWARD
Haumschild suggests creating a tip sheet detailing the largest payers and their preferred oncology agents. He also explained that it is important to create a secondary process so that if the provider receives an insurance denial, there is an efficient method for swapping medication decisions and updating clinical data in real time to keep safety as a primary factor for all decisions. He also highlighted the importance of creating strategies to maintain financial sustainability.

“I would also say that with specialty pharmacy, you need to make sure that your health system specialty pharmacy has access to limited distribution medications because there are data out there that show that health systems and specialty pharmacies provide a higher touch of care, they provide more integrated care, and they can come up with better outcomes for those patients,” Haumschild said.

“Outpatient infusion center pharmacies must prepare for the shift from a revenue focus to a cost-outcomes focus,” Soefje noted. “We also have to think in a big picture mode, in that it might be appropriate to spend more on a drug if it prevents a hospitalization or an emergency department visit. Value will be the key. Everything that an institution does will need to be valuable to someone, and that value needs to be measured and reported.”

Haumschild also highlighted the importance of assessing outcomes. “If we are going to operate with the best care for our patients and the best outcome, we can’t just talk about the models and explain them, but we actually have to show the outcomes and show how the outcomes are better,” Haumschild explained. “And I think that’s really where the value proposition will be at the forefront of the patient and the practice.”

“It will be a difficult balance to improve throughput in the clinic, while at the same time assuring the patient feels they have received the care they want,” Soefje said. “Value cannot be reiterated enough. We have to eliminate the waste in health care and ensure that the outcomes are maximized while we reduce the total cost of care.”

For a full list of references, see the article at OncLive.com.
Financial Steps to Save Your Practice During the COVID-19 Pandemic

by TODD SHRYOCK

THE OUTBREAK OF THE CORONAVIRUS disease 2019 (COVID-19) is having a financial impact on both private practices and oncology practices nationwide. Experts say many practices are seeing a decline in patient volume as people avoid doctors’ offices unless they have no other choice.

Right now, there are so many unknowns that keeping a practice profitable is a daunting challenge. If the crisis lasts for months, as many expect, it could threaten the viability of practices that were already struggling as patient volume continues to decline. Experts say practice leaders need to accept that their organizations are most likely going to take a financial hit and should start planning accordingly.

“This could have a major impact on each practice,” said Owen Dahl, MBA, FACHE, a medical practice management consultant. “Throw in an employee who gets the virus or has to stay home because of their kids, and it could become a major issue.”

Planning for Practice Survival

Dahl said to start running projections on what the practice finances would look like if revenue dropped 10%, 20%, 50%, or even 80%. “Building proformas on what the impact would be is critical,” he said. “Start there, then look at what patients you need to see and what you can do to generate revenue in some fashion.” With the loosening of telehealth restrictions, some practices may be able to keep patient volume up while still receiving reimbursement by Medicare and commercial payers.

“You have to really overplan at this point,” said Joseph Valenti, MD, board member of The Physicians Foundation. “We could really be looking at many months of problems, and a lot of practices may not survive that. We can’t get into a situation as a nation where physicians are unable to keep the doors open financially and are unable to take care of patients when they most need them.”

Expenses need a careful review after the projections are complete. “You may have to lay off employees or rotate staff to work alternating days,” said Dahl. “You don’t want to lose staff if you can help it because you will need them to recover.”

If a practice doesn’t have a line of credit, Dahl said, now is a good time to apply for one. The money could be the difference between practice survival or going out of business. “It’s for these kinds of emergency situations.” The proforma projections will help determine where the money needs to be spent.

Valenti said a Small Business Administration loan is another option if a line of credit is not available and that doctors should not be reluctant to reach out to vendors to renegotiate or ask for more repayment time. Because some vendors will not send more products if payments are in arrears, Valenti says it is important to reach out and explain the situation to see if they will grant an exception.

“The same thing goes with rent—you may need to ask for a lease abatement,” he adds. “You have to make your practice as trim and fit as possible. All you can do is ask, and the worst thing they can say is no.”

Professional associations can help as well, and some are providing resources and guidance to their members during the emergency, said Lisa Stevens Anderson, president of Equality Health’s Management Services Organization division. For example, the American Academy of Family Physicians recently called on Congress to establish a 24-month, interest-free loan program for small and independent practices that have been negatively affected by the COVID-19 crisis. The American Academy of Family Physicians has also called for provisions that would require Medicaid to reimburse at Medicare rates and has also asked for a grant fund so that small practices could purchase telehealth equipment.

Doctors should also look at a worst-case scenario. If the practice had to close because too many employees are sick, or all the doctors are sick, it could trigger business interruption insurance coverage. Dahl said to make sure to understand what is and isn’t covered and prepare accordingly.

Teamwork and Focus

Boosting staff morale is also key to maintaining focus on patient care and getting everyone to work toward keeping the practice open.

“I think it’s important, so say to the staff: ‘Let’s get through today and not think about the future, but 2 to 4 weeks from now, let’s start to think about what the future holds,’” said Dahl. “What does it hold and how can we make sure we improve care and come out of this whole?”

“Recognize the stress the staff is under,” said Anderson. “Make regular, timely communications about efforts to maintain the office, take care of patients, and maintain financial viability. If employees don’t have information, they get scared.”

If staff cuts are being considered, Anderson says to explain the situation to the staff and see if they have any ideas. Instead of assuming no one wants their hours reduced, for example, someone may volunteer because of their current life circumstances. “If you can stay connected during this time, you can increase and reinforce their loyalty,” she said.

Valenti said that the crisis might help reaffirm the important role of physicians in the health care system. “With the relaxation of some of the CMS [Centers for Medicare & Medicaid Services] rules, I think we are about to demonstrate why overregulation is not a good thing,” he said. “We all need some regulation, but when it’s overdone, it hinders our ability to practice and we become less efficient. I think deregulating some of these things during the pandemic will prove we don’t really need them.”
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Seeking a New Path for AL Amyloidosis

by GIADA BIANCHI, MD

SYSTEMIC AMYLOIDOSIS is a heterogeneous family of diseases characterized by deposition of fibrillary aggregates of a precursor protein in target organs, such as the heart and kidneys (FIGURES 1 AND 2). The identity of the amyloidogenic precursor protein, such as transthyretin (TTR) or immunoglobulin light chain (AL), dictates the pattern of organ deposition and clinical presentation and determines the therapeutic approach (ie, chemotherapy or chemoimmunotherapy for AL versus TTR stabilizer or gene silencing for TTR amyloidosis). AL amyloidosis is the most common form of systemic amyloidosis and is characterized by rapidly progressive organ failure and eventually patient demise, if not promptly recognized and treated. The pathogenetic mechanism in AL amyloidosis is deposition of fibrils of misfolded immunoglobulin free light chains (FLC), typically produced by clonal plasma cells and, less often, B cells.

The FLC is λ in 75% of cases and a small pool of Ig light chain variable (IGVL) genotypes underlies most AL amyloidosis cases, suggesting that amyloidogenicity is an intrinsic characteristic of the amino acid sequence of the FLC. Progression of AL amyloidosis from precursor plasma cell dyscrasia such as monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM) can occur and hematologists must carefully monitor these patients for signs or symptoms concerning AL amyloidosis.

NAVI GATING THE AL MAZE

Epidemiologic studies suggest that AL amyloidosis is not a rare disease, but rather underdiagnosed. The vague nature of early symptoms, such as fatigue and weight loss, contributes to diagnostic delay, potentially causing irreversible organ damage and high risk of early mortality. There is no FDA-approved treatment for AL amyloidosis; however, chemotherapy targeting plasma cells, such as cyclophosphamide, bortezomib (Velcade), and dexamethasone (CyBorD), and/or autologous stem cell transplant, are standard of care and can elicit deep and durable hematologic responses. Chemotherapy does not directly target the deposited amyloid fibrils but it halts progressive organ dysfunction by abating FLC secretion and thus amyloid deposition. In patients who achieve a hematologic remission, the deposited amyloid is then removed over a period of months or years. The causes of inefficient amyloid removal remain poorly understood.

Clinical research efforts in AL amyloidosis have focused on 3 main areas: (1) early diagnosis; (2) effective chemotherapy; and (3) antifibrillar drugs (FIGURE 3). With the FDA approval of inotersen (Tegsedi) and patisiran (Onpattro) for hereditary TTR amyloidosis (ATTR)-related neuropathy and tafamidis (Vyndamax) for ATTR-related cardiomyopathy, it has become even more critical to accurately distinguish ATTR versus AL amyloidosis.

Significant epidemiological and clinical overlap exists for ATTR and AL amyloidosis and an expedited, careful diagnostic work up with definitive confirmation of precursor amyloid protein via liquid chromatography and mass spectrometry (LC-MS) or immunogold on tissue biopsy is thus critical. Research efforts to identify MGUS/SMM patients at high risk for AL amyloidosis transformation include the study of serum FLC N-glycosylation via LC-MS and in vitro fibrillogenic competition assay with circulating FLC. The SAVE clinical study (NCT02741999) evaluates asymptomatic patients with a provisional diagnosis of light chain MGUS/SMM to identify IGVL genotypes associated with highest risk of amyloidogenicity and ensure patients are screened accordingly. Innovative molecular imaging modalities detecting AL fibrils in a highly specific manner are being investigated as a tool to assess amyloid deposition and distribution even before overt clinical manifestations.

CHALLENGES IN TREATING PATIENTS

The major hurdle in treating patients with AL amyloidosis using multiple myeloma (MM)-directed chemotherapy is decreased tolerance, particularly in patients with advanced cardiomyopathy or nephrotic syndrome, rather than lack of efficacy. As a single agent, the CD38-targeting antibody daratumumab (Darzalex) has shown unprecedented effectiveness in inducing rapid and profound hematologic responses in patients with heavily pretreated AL amyloidosis, but large volume infusion and high steroid dosing limited tolerability. Excitingly, the FDA approved the subcutaneous formulation of fixed dose daratumumab and hyaluronidase-fihj (Darzalex Faspro) for all previously approved indications of intravenous daratumumab.

The ANDROMEDA trial (NCT03201965), a phase 3, randomized trial comparing CyBorD alone or in combination with subcutaneous daratumumab, closed to accrual in August 2019. Data on the 28 patients enrolled in the safety run-in phase showed an overall response rate of 96% with 82% of those very good partial responses or better, including 36% complete responses. The quadruple combination was well tolerated overall and may become frontline, standard of care. The phase 3 TOURMALINE-AL1 trial (NCT01659658) that randomized patients to receive either ixazomib (Ninlaro) plus dexamethasone or clinician’s choice was closed early due to lack of significant improvement in overall hematologic response. However, patients in the ixazomib arm enjoyed a doubling of hematologic response duration compared with controls (46.5 vs 20.2 months, respectively).
FIGURE 1. Histopathologic Appearance of Cardiac Amyloidosis

Panel A: Congo red staining of endomyocardial biopsy specimen demonstrating positive staining of amyloid depositing individual cardiac myocytes. Panel B: Congo red stain of same specimen observed under polarized light showing apple green birefringence of amyloid deposits. Panel C: Hematoxylin and eosin staining of endomyocardial biopsy showing an arteriole with amyloid deposition leading to wall thickening and stenosis. Panel D: Sulfated Alcian blue staining of endomyocardial arteriole outlining the amyloid in blue-green. (Images courtesy of Robert F. Padera, Jr, MD, PhD)

FIGURE 2. Histopathologic Appearance of Renal λ Light Chain AL Amyloidosis


FIGURE 3. Critical Areas of Research Effort in AL Amyloidosis

Venn diagram showing the 3 main areas of effort in the amyloid research community. Blue indicates early diagnosis: the use of novel tools and technologies to identify patients with AL amyloidosis before overt organ dysfunction occurs. Pink indicates effective chemotherapy: the clinical research effort identifying the most active and tolerated regimens. Yellow indicates antifibrillary antibodies: the use of immunotherapy to facilitate the reabsorption of deposited amyloid fibrils. At the center, the overall goal of this effort: improving outcome by abating early mortality and extending survival in our patients with AL amyloidosis.

suggesting a potential role for ixazomib as maintenance therapy.25

Translocation t(11;14) is the most common cytogenetic abnormality in AL amyloidosis and is present in approximately 40% of patients. It is a poor prognostic factor for overall survival and a negative predictive factor of response to bortezomib-containing regimens.26 However, in MM, t(11;14) is a biomarker of high BCL-2 expression and a predictive factor of response to the BCL-2 inhibitor venetoclax (Venclexta).27 Several clinical trials of venetoclax in MM have been halted due to excess mortality from infectious complications noted in patients receiving venetoclax in combination with bortezomib and dexamethasone in the phase 3 BELLINI study (NCT02735597).28

As benefits seem to outweigh risks for patients with t(11;14), the amyloidosis community is eagerly awaiting the FDA to lift the hold so that venetoclax can be tested in clinical trials in patients with t(11;14) AL amyloidosis. The BCMA-targeting antibody-drug conjugate belantamab mafodotin and melphalan, a melphalan derivative, showed promising results in MM, and clinical trials are underway or anticipated in AL amyloidosis.29-31

LOOKING AHEAD

Although overall survival of patients with AL amyloidosis has substantially improved thanks to more effective chemotherapy, early mortality remains largely unaffected and mostly related to delayed diagnosis leading to advanced cardiac dysfunction. Thus, a significant research effort has been funneled toward developing therapeutics to facilitate the reabsorption of deposited amyloid. The antimicrobial doxycycline was shown to rescue cardiomyocyte from direct FLC toxicity and to interfere with fibrillogenesis in preclinical models.32,33

Retrospective and phase 2 studies confirmed that adding doxycycline to standard chemotherapy reduces early cardiac mortality and its use is suggested in patients with AL amyloidosis-related cardiomyopathy in combination with chemotherapy.34,35 The antifibrillary antibody birtamimab (NEO001) showed promising results in improving cardiac dysfunction in early-phase clinical studies.36 However, drug development was halted based on lack of benefit in a large phase 3 study.37

In a phase 1a/b study enrolling patients with relapsed/refractory AL amyloidosis, CAEL-101, a novel antibody recognizing an epitope solely exposed by misfolded FLC, showed rapid and frequent cardiac and renal responses independently of hematologic response with no patient experiencing organ progression while they were on the study.38 A phase 2/3 study (NCT04304144) of CAEL-101 in combination with CyBorD in patients with treatment-naive AL amyloidosis with cardiac dysfunction is currently recruiting.

The upfront use of antifibrillary antibodies and highly effective, combinatory chemotherapy could profoundly affect the natural history of this devastating condition and finally improve early mortality. Together with an effort to educate clinicians to think about amyloidosis in their daily practice, studies focusing on early recognition or diagnosis in high-risk groups such as African Americans and patients with a preexisting MGUS/SMM diagnosis are likely to have a major impact from a public health standpoint.

This is an exciting time for the AL amyloidosis community as patient advocacy groups, academia, pharmaceutical companies, and regulatory agencies are joining in an effort to develop safe and effective treatments for patients with AL amyloidosis.
Up to half of patients with HER2-positive metastatic breast cancer (MBC) treated with trastuzumab (Herceptin)-based therapy will develop breast cancer brain metastases (BCBMs). Women with early-stage HER2-positive breast cancer treated in the adjuvant setting with trastuzumab-based therapies and/or ado-trastuzumab emtansine (T-DM1; Kadcyla) are at risk of developing BCBMs, which are often the only site of recurrence.

Isolated intracranial recurrence remains a clinical problem in the early stage and advanced setting and is likely due to poor central nervous system (CNS) penetrability of the best available HER2-targeted agents used in HER2-positive early-stage MBC (trastuzumab, pertuzumab [Perjeta], and T-DM1). First-line treatment of HER2-positive MBC includes taxane-based chemotherapy added to trastuzumab (T) and pertuzumab (P) for at least 6 cycles followed by TP alone (with the addition of endocrine therapy for patients with hormone receptor–positive disease).

The addition of pertuzumab to taxane/trastuzumab has increased time to BCBM development in the first line and has improved overall survival (OS) in patients who progress and develop BCBMs. This was demonstrated in the phase 3 CLEOPATRA trial (NCT00567190), which tested the regimen in MBC. Patients with baseline BCBMs were not included in the study population. T-DM1 is the current standard-of-care second-line treatment for patients with HER2-positive MBC due to its superiority over capecitabine/lapatinib demonstrated in the EMILIA clinical trial (NCT00829166). Patients with stable and treated baseline brain metastases were included in this clinical trial. Among patients with BCBM at baseline, there was a significant improvement in OS observed in the T-DM1 arm compared with the capecitabine/lapatinib arm (HR, 0.38; \( P = .008 \); median, 26.8 vs 12.9 months). At this time, for most patients, first- and second-line treatments for HER2-positive MBC are the same regardless of the presence or absence of brain metastases.

In the third-line setting and beyond, we have several options with clear evidence of intracranial efficacy in the treatment of HER2-positive BCBMs (FIGURE). Our arsenal of highly effective, targeted agents including tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates for the treatment of HER2-positive MBC in the third line and beyond has expanded by more than 50% in the past year.

The combinations of neratinib (Nerlynx)/capecitabine, tucatinib (Tukysa)/trastuzumab/capecitabine, and fam-trastuzumab deruxtecan-nxki (Enhertu) have all shown impressive results in the past year for patients with HER2-positive BCBMs. Given these breakthroughs that have broadened the arsenal of treatment options for our patients, oncologists are now left with uncertainty about how to best sequence therapies for patients with HER2-positive BCBMs that will optimize both intracranial and extracranial progression-free survival (PFS), and OS, especially in the third-line setting and beyond. Choice of and sequencing of therapy between neratinib/capecitabine, tucatinib/trastuzumab/capecitabine; and trastuzumab-deruxtecan generally depends on stable versus progressive nature of brain metastases, prior systemic treatments, state of extracranial disease status, and diverse toxicity profiles.
WHAT TO DO WITH FIRST INTRACRANIAL RECURRENTNESS? Initial treatment for BCMBs in patients with HER2-positive breast cancer traditionally includes local therapies, such as neurosurgical resection and/or radiation therapy (stereotactic radiosurgery vs whole brain radiation). Resection is considered with a single, space-occupying brain metastasis when systemic disease is otherwise stable in patients with a good performance status. Stereotactic radiosurgery is the preferred radiation modality for a limited number of brain metastases. Current national guidelines recommend local therapy to the existing brain metastases and to continue on current HER2-targeted systemic therapy if extracranial disease is stable or absent. Six hundred twenty-one patients were randomized in a 1:1 fashion.

For example, patients receiving first-line TP would receive upfront local therapy and then continue on TP if extracranial disease is stable or absent. Upon second and third intracranial recurrence, the treatment course is highly patient-specific, and there is no single consensus on local therapy or systemic treatment recommendations. Multidisciplinary evaluation is recommended.

NERATINIB AND CAPECITABINE

Neratinib is an oral, irreversible, TKI with activity against HER1, HER2, and HER4. Neratinib has shown intracranial efficacy and blood-brain-barrier penetration in preclinical models. The Translational Breast Cancer Research Consortium 022 trial (TBCRC 22; NCT01494662) is a phase 2, open label clinical trial of neratinib 240 mg once daily plus capecitabine 750 mg/m² twice daily for 14 days on/7 days off. A strength of this study is that patients have to have measurable and progressive HER2-positive BCMBs after local therapy.

Forty-nine patients enrolled in cohorts 3A/ lapatinib-naïve (n = 37) and 3B/prior lapatinib (Tykerb) (n = 12; cohort closed for slow accrual). The CNS ORR was 49% in cohort 3A (95% CI, 32%-66%) and 33% in cohort 3B (95% CI, 10%-65%). Median PFS was 5.5 and 3.1 months in cohorts 3A and 3B, respectively. Of note, single-agent neratinib was studied with minimal efficacy.

NALA (NCT01808573) was a phase 3 international, randomized clinical trial of neratinib plus capecitabine (N+C) versus the reversible dual TKI lapatinib plus capecitabine (L+C) in patients with HER2-positive MBC who had received at least 2 prior HER2-directed regimens. Six hundred twenty-one patients were randomized in a 1:1 fashion.

The PFS was 8.8 months versus 6.6 months favoring N+C. Six- and 12-month PFS rates were 90.2% versus 87.5% and 72.5% versus 66.7% for N+C versus L+C, respectively (HR, 0.88; 95% CI, 0.72-1.07; P = .2086). OS was similar between arms. Clinical benefit rate (44.5% vs 35.6%; P = .0328) and duration of response (HR, 0.50; 95% CI 0.33-0.74; P = .0004) favored N+C. Time to intervention for symptomatic CNS disease (overall cumulative incidence 22.8% vs 29.2%; P = .043) was delayed with N+C versus L+C. Importantly, there was a higher rate of grade 3 diarrhea with N+C versus L+C (24.4% vs 12.5%). Based on results of the phase 2 CONTROL study (NCT02400476), rates of grade 3 diarrhea can be more effectively managed with prophylactic loperamide and the addition of colestipol to improve gastrointestinal toxicity. The FDA approved neratinib for HER2-positive MBC on February 26, 2020, for patients who have received at least 2 lines of anti-HER2-based regimens in the metastatic setting.

CONCLUSION

The accumulation of data suggests that neratinib and capecitabine together have intracranial efficacy in both stable and progressive brain metastases in patients who have received at least 2 prior HER2-directed regimens. Intracranial response is superior in a lapatinib-naïve population but is still respectable in a lapatinib-treated population. Diarrheal prophylaxis is paramount for tolerability of this combination.

TUCHARINIB

Tucatinib is an oral, potent, HER2-specific reversible TKI, demonstrating preclinical intracranial activity when used with standard doses of capecitabine and trastuzumab. In 2 phase 1b dose-escalation trials, tucatinib in combination with either trastuzumab/capecitabine, trastuzumab alone, or T-DM1 showed encouraging intracranial disease activity and control in patients with untreated, progressive, or stable HER2-positive metastases.

Furthermore, practice-changing results were recently reported for the phase 2, randomized, multicenter, international, HER2CLIMB trial (NCT02614794) in patients with HER2-positive MBC that were treated with the addition of tucatinib to trastuzumab and capecitabine versus trastuzumab, capecitabine, and placebo. All patients in this trial had received previous TP and T-DM1; therefore, the regimen was beyond second line. Patients with stable untreated, treated progressive, and stable treated brain metastases were well-represented, a novel inclusion criterion for a phase 2 clinical trial in MBC.

The addition of tucatinib improved both PFS and OS in the intention-to-treat population and the population with BCMBs. For the patients with brain metastases (47% of participants), the addition of tucatinib resulted in a 52% reduction in disease progression or risk of death (HR, 0.48; 95% CI, 0.34-0.69; P < .00001). Among the 511 patients with measurable disease, the
percentage who had a confirmed objective response was 40.6% (95% CI, 35.3%-46.0%) in the tucatinib-combination group and 22.8% (95% CI, 16.7%-29.8%) in the placebo-combination group (P < .001).

The FDA approved tucatinib in combination with trastuzumab and capecitabine on April 17, 2020, for the treatment of patients with HER2-positive MBC, including patients with brain metastases who have received 1 or more prior anti-HER2 based regimens in the metastatic setting.

**CONCLUSION** Tucatinib in combination with trastuzumab and capecitabine is an excellent option for women with HER2-positive BCBM after progression of pertuzumab, trastuzumab, and T-DM1. Sequencing of tucatinib prior to or in combination with T-DM1 is an area of active research. Our preference would be to enroll patients in the ongoing, phase 3 clinical trial of T-DM1 with or without tucatinib that allows patients with brain metastases (NCT03975647).

**TRASTUZUMAB DERUXTECAN**

Trastuzumab deruxtecan is an antibody-drug conjugate including an anti-HER2 monoclonal antibody, a cleavable tetrapeptide-based linker, and a healthy payload of cytotoxic topoisomerase I inhibitor. It has a higher drug-to-antibody ratio than T-DM1 (approximately 8 vs 3-4, respectively).

DESTINY-Breast01 (NCT03248492) was a 2-part, open-label, single-group, multicenter study of trastuzumab deruxtecan in adults with pathologically documented HER2-positive, unresectable MBC who had received previous treatment with T-DM1. In total, 184 heavily pretreated patients (median 6 previous treatments) received trastuzumab deruxtecan 5.4 mg/kg. In the intention-to-treat analysis, a response to therapy was reported in 112 patients (60.9%; 95% CI, 53.4%-68.0%). The median response duration was 14.8 months (95% CI, 13.8-16.9), and the median duration of PFS was 16.4 months (95% CI, 12.7-not reached).

This is an unprecedented finding in such a heavily pretreated population. Patients on this study could have stable brain metastases; untreated or symptomatic brain metastases was an exclusion criterion. In total, 24 patients with stable brain metastases were included and, among those, the median PFS was 18.1 months (95% CI, 6.7-18.1). Intracranial efficacy was not tracked formally. Pneumonitis is a serious adverse event observed with trastuzumab deruxtecan.

**CONCLUSION** Further studies are needed to understand intracranial efficacy of this compound and optimal usage in patients with untreated or progressive brain metastases despite prior local therapy. Trastuzumab deruxtecan is an excellent option for patients with stable/treated brain metastases and no history of pneumonitis.

**THE BIGGER PICTURE**

At the current time, the recommended first- and second-line treatment of patients with HER2-positive MBC and brain metastases remains the same as those without brain metastases: (1) taxane/trastuzumab/pertuzumab (2) T-DM1. Pertuzumab added to trastuzumab and a taxane prolonged survival in patients who eventually went on to develop BCBM. T-DM1 improved overall survival in patients with baseline stable/treated brain metastases over capecitabine/lapatinib in the second-line setting in a subgroup analysis. Tucatinib added to trastuzumab and capecitabine was recently approved after 1 prior line of HER2-targeted therapy; however, all patients in the pivotal trial had received both prior TP and T-DM1.

Studies are ongoing and in the planning phases to determine the impact of moving tucatinib, in combination with HER2-targeted agents, earlier in the traditional treatment sequence, particularly for those with BCBM. We would encourage participation in these important clinical trials to gain evidence-based guidance.

Upon first intracranial progression, CNS-directed, local therapy is typically recommended for the majority of patients. Systemic therapy following local therapy has been shown to improve survival and is recommended pending the patient’s performance status.13 Treatment choice largely depends on the status of extracranial disease. If the patient is stable or if there is no evidence of disease, continuing current therapy at first intracranial progression is preferred. If extracranial disease is progressive, advancing to the next line of therapy is recommended. Upon further intracranial progressions, recommendations are patient-specific and tailored by prior CNS and systemic treatments, patient performance status, and adverse event profiles. It is increasingly appealing to introduce highly effective, CNS-penetrant drugs such as tucatinib into the earlier settings in patients whose intracranial disease is the primary disease site. A phase 3 clinical trial of tucatinib added to T-DM1 is ongoing and is enrolling patients with untreated, stable, or progressive brain metastases (NCT03975647).

We now have several good options beyond the second-line setting for patients with HER2-positive BCBM (FIGURE).

Factors paramount in determining which agent to select and when include both extracranial disease status and the status of intracranial disease—stable and treated, treated and progressive, or asymptomatic and untreated. For patients with stable brain metastases after local therapy who are progressing extracranially, tucatinib/trastuzumab/capecitabine or trastuzumab deruxtecan are both reasonable choices. For patients with rapid, visceral progression in need of a robust response, the overall response rate of trastuzumab (61%) is superior to HER2-directed TKIs, with corresponding duration of response approaching a year and half. Trastuzumab deruxtecan has yet to be formally studied in patients with treated, but progressive, or previously untreated brain metastases and intracranial response remains unknown.

Finally, tucatinib/trastuzumab/capecitabine and neratinib/capecitabine have both illustrated efficacy in treated, but progressive or untreated brain metastases; however, these regimens have not been compared head to head. It is important to note that activity of neratinib/capecitabine after lapatinib is more limited.

Collectively, there are more options than ever in the space of HER2-positive BCBM, a significant advance for our hundreds and thousands of patients facing this challenging disease. Our goal now is to determine the optimal combination and sequence of therapies to extend survival in a meaningful way. Continued development of rationally designed clinical trials, and integrating systemic and local therapies, will lead the way forward.
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A New Generation of Drugs Targeting PD-1/PD-L1 Takes Shape

by JANE DE LARTIGUE, PHD

OVER THE PAST DECADE, immunotherapy has established itself as one of the pillars of cancer treatment, thanks in large part to the success of monoclonal antibodies (mAbs) that target the immune checkpoint protein PD-1 or its main ligand, PD-L1.1 The FDA has approved 6 anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs) covering 16 cancer indications as monotherapy or in combination with other drugs. ICIs also made history for having the first tissue-agnostic indications, with several agents approved across cancer types with microsatellite instability-high (MSI-H) or DNA mismatch repair–deficient (dMMR) biomarkers.2,3

Now a new generation of ICIs targeting the PD-1/PD-L1 pathway is in the works, with numerous drug companies trying to develop their own offerings (TABLE). According to a recent analysis, nearly 3000 clinical trials testing PD-1/PD-L1 inhibitors were recruiting participants across most cancer types as of September 2019, with a total target enrollment of more than half a million patients.2

Biotechnology companies based in China are particularly active in the field. Chinese regulators have approved 4 PD-1 inhibitors developed domestically in addition to agents from international pharmaceutical firms,4-6 and several other novel therapies are in late-stage clinical testing.

In an increasingly crowded space, the focus is on novel strategies that might help a drug stand out from the crowd while also addressing limitations of ICI efficacy. Accordingly, 76% of ongoing clinical trials of PD-1/PD-L1 inhibitors involve combination therapy, predominantly with chemotherapy, tyrosine kinase inhibitors, and other types of ICIs.2 Investigators are also using new drug designs to combine different mechanisms into a single molecule. Bispecific antibodies and fusion proteins are demonstrating early promise across several tumor types.

Yet the dizzying pace of drug development has been curbed in recent months by the coronavirus disease 2019 pandemic. Regulatory agencies are providing assistance, and other government agencies have released guidance for investigators whose trials are affected. Nonetheless, these are challenging times, with patients reluctant to enroll in trials or unable to reach hospitals, in addition to laboratories being shut down and investigators retasked to serve on the front lines. Globally, companies have had to modify or even halt ongoing clinical trials, and the future is likely to be uncertain for some time.9,10

THE CHECKPOINT IN ACTION

The cancer immunologist George Klein wrote that “cancer derives from self-somatic cells, and therefore cancer immunity is a matter of breaking self-tolerance, which is a difficult proposition.” The discovery of the PDCD1 gene in the 1990s has brought the oncology community a long way toward achieving that challenging goal.11-13

PDCD1 encodes PD-1, a type I transmembrane receptor originally identified as being involved in the programmed cell death of immune cells. The receptor has subsequently been shown to play an important role in the checks and balances on the immune system that maintain self-tolerance to prevent collateral damage from the immune response, such as that seen in autoimmune diseases.11,13,14

PD-1 is a member of the B7/CD28 family of receptors that share a common structure: an immunoglobulin-like extracellular domain, a transmembrane domain, and an intracellular...
domain containing the immunoreceptor tyrosine-based inhibitory and signaling motifs (ITIM and ITSM, respectively).\textsuperscript{13,15-17}

ITIM and ITSM are phosphorylated when PD-1 is engaged by either of its ligands, PD-L1 or PD-L2, leading to recruitment of the SRC homology phosphatases SHP1 and SHP2, which transmit the signal into the cell. PD-1 is predominantly expressed on activated T cells, the major cytotoxic effectors of the adaptive immune response, and the signal it transmits helps to damp down the T-cell-mediated immune response.\textsuperscript{13,15-17}

Two separate signals are required to fully activate T cells that keep cytotoxic activity in check. The first comes from the interaction between the T-cell receptor and major histocompatibility complex-presented antigen epitopes on the surface of an antigen-presenting cell (APC). The second comes from engagement of costimulatory receptor-ligand pairs on the T-cell and APC surfaces (\textbf{FIGURE}13,15-17). PD-1 belongs to a group of coinhibitory receptors that regulate T-cell activity via ligand binding, which can drive T cells into a state known as exhaustion, in which they are unable to proliferate or perform their effector functions.\textsuperscript{13,15-17}

PD-L1 and PD-L2 are also transmembrane proteins that are identical in almost 40% of their amino acid sequence but differ in their affinity for PD-1 and the cell types and tissues in which they are expressed, with PD-L1 expression more widespread. They are characteristically constitutively expressed on the surface of APCs. However, their expression can also be induced on other cell types in response to inflammatory signals.\textsuperscript{13,15-17}

\textbf{BREAKING SELF-TOLERANCE}

As Klein pointed out, tumors develop from the body’s own cells and should not provoke an immune response; however, many of the aberrant cellular processes that drive cancer development generate unusual proteins that can be recognized by the immune system as foreign antigens. Although this immune surveillance can eliminate cancer cells, selective pressure can ultimately cause them to evade the antitumor immune response through a variety of mechanisms. Indeed, immune evasion is now widely recognized as a hallmark of cancer.\textsuperscript{18,19}

Exploitation of immune checkpoints like PD-1 is one of these mechanisms. PD-L1 is overexpressed on the surface of many different tumor types, including melanoma, lymphomas, and lung, breast, bladder, kidney, and brain tumors. This enables tumors to engage any T cells that infiltrate them and essentially switch them off.\textsuperscript{13,15-17}

PD-L1 expression in tumors can be constitutive, as a by-product of oncogenic driver mechanisms, or induced by upregulated inflammatory signals produced by the tumor microenvironment. PD-L1 can also be expressed by myeloid cells in the tumor microenvironment, such as macrophages and dendritic cells.\textsuperscript{13}

\textbf{ANTIBODY DEVELOPMENT}

The clinical success of mAbs targeting PD-1 and PD-L1 is an attractive lure, and drug development in this sphere continues at a robust pace. Numerous companies headquartered in the United States and Europe have entered the game, with their own PD-1 and PD-L1 mAbs in clinical development. But fierce competition is driving them to seek new ways to differentiate themselves.

\textbf{Spartalizumab}

One way to distinguish these agents is to pursue combination therapies that might expand the efficacy of PD-1/PD-L1 therapy, which is not effective in all patients. Notable in this respect is Novartis’ spartalizumab (PDR001), a humanized immunoglobulin (Ig) G4-based PD-1-targeted mAb.\textsuperscript{20} Early findings from the phase 3 COMBI-i trial (NCT02967692) evaluating melanoma treatment with spartalizumab, in combination with the BRAF inhibitor dabrafenib (Tafinlar) and the MEK inhibitor trametinib (Mekinist), continue to show promising efficacy, according to updated results from the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting.\textsuperscript{21}

Pooled data from 36 patients enrolled in run-in and biomarker cohorts demonstrated an investigator-assessed objective response rate (ORR) of 78%, including 44% with complete responses (CRs). Median duration of response had not been reached after a median follow-up of 24.3 months, but the 24-month rate was 53.4%. The median progression-free survival (PFS) was 22.7 months, and the median overall survival (OS) had not been reached.

Grade 3 and higher treatment-related adverse events (TRAEs), most commonly pyrexia, neutropenia, and increased lipase levels, occurred in 72% of patients, and 17% of patients experienced events that led to discontinuation of all 3 study drugs.\textsuperscript{21}

COMBI-i is continuing as a randomized study in which approximately 500 patients with previously untreated resectable metastatic \textit{BRAF} V600-mutated melanoma will receive either the triplet therapy that includes spartalizumab or doublet therapy with the 2 targeted agents.

\textbf{Dostarlimab}

Tesaro, which GlaxoSmithKline acquired in 2019,\textsuperscript{22} has developed the humanized anti-PD-1 IgG4 mAb dostarlimab (TSR-042). Several phase 3 clinical trials are ongoing, including in patients with endometrial cancer. Investigators presented results from cohorts of patients with endometrial cancer treated in the phase 1/2 GARNET trial (NCT02715284) at the 2019 Society of Gynecologic Oncology Annual Meeting on Women’s Cancer.

Participants (\textit{N} = 110) received dostarlimab 500 mg every 3 weeks for the first 4 cycles and then 1000 mg every 6 weeks thereafter. Overall, the ORR was 27.7% and the disease control rate was 48.9%, with ongoing responses at data cutoff in most patients who exhibited a response. However, patients with MSI-H tumors had a particularly impressive ORR of 50% compared with 19.1% in patients with microsatellite-stable disease.\textsuperscript{23} In an updated interim analysis published in March 2020, the ORR was 43% among GARNET participants (\textit{N} = 70) with dMMR disease and at least 6 months of follow-up at the data cutoff of July 8, 2019.\textsuperscript{24}

\textbf{Cosibelimab}

Checkpoint Therapeutics is developing cosibelimab (CK-301), a fully human IgG1 mAb against PD-L1.\textsuperscript{13,14} Investigators presented positive interim data from a first-in-human study (NCT03212404) at the 2019 European Society for Molecular Oncology meeting. At the data cutoff in August 2019, 68 patients had at least 2 tumor assessments or had discontinued treatment, and the ORR across tumor types was 27.9%. The ORRs in cohorts of patients with cutaneous squamous cell carcinoma (CSCC; \textit{n} = 14) and non-small cell lung cancer (NSCLC; \textit{n} = 25) were 50% and 40%, with ongoing responses in 100% and 90% of responders, respectively.

Grade 3 or higher TRAEs occurred in 33.3% of patients. The most common any-grade...
TRAEs were rash, fatigue, hypothyroidism, anemia, elevated alanine aminotransferase levels, diarrhea, and infusion-related reaction. Checkpoint Therapeutics reported that based on positive feedback from the FDA, it intends to submit cosibelimab for approval as a CSCC treatment based on data from this trial.

EAST MEETS WEST
As Western markets become increasingly saturated with PD-1/PD-L1 inhibitors, pharmaceutical companies are seeking to expand into new areas, particularly in China and other Asian countries. Nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq), and durvalumab (Imfinzi) were recently approved by the Chinese regulatory agency, the National Medical Products Administration (NMPA). The approvals were for single indications (lung cancer), except pembrolizumab, which became the first to secure 2 approved indications in China (NSCLC and melanoma).

With China’s status as the second-leading pharmaceutical market and foremost emerging

| TABLE. Select Emerging Drugs Aimed at PD-1/PD-L1 Activity in Development |
|-----------------------------|-----------------------------|
| **Drug (developer)**        | **Most advanced development stage and cancer types** |
| Humanized IgG4 anti-PD-1 mAb |                                            |
| Camrelizumab (AiRuiKa; SHR-1210) (Jiangsu Hengrui Medicine) | Approved in China (HL) |
| Tislelizumab (BGB-A317) (BeiGene/Cellgene) | Approved in China (HL and urothelial carcinoma) |
| Toripalimab (Tuying; JS001) (Shanghai Junshi Biosciences) | Approved in China (melanoma) |
| Spartalizumab (PDR001) (Novartis) | Phase 3 with US locations: melanoma (COMBI-v; NCT02967692) |
| Dostarlimab (TSR-042) (Tesaro, GlaxoSmithKline) | Phase 3 with US locations: endometrial cancer (RUBY; NCT03981796), nonmucinous EOC (FIRST; NCT03602859) |
| MGA012 (INCMGA00012) Incyte/MacroGenics | Phase 2/3 in France: endometrial or ovarian carcinosarcoma |
| Sasanlimab (PF-06801591) (Pfizer) | Phase 3 with US locations: high-risk non–muscle-invasive bladder cancer (B0011006; NCT04165317) |
| Budigalimab (ABBV-181) (AbbVie) | Phase 1 with US locations: advanced solid tumors (NCT03821935, NCT03000257, NCT02988960, NCT03893955), SCLC (NCT03639194) |
| BI 754091 (Boehringer Ingelheim) | Phase 2 with US locations: advanced solid tumors (NCT03697304) |

**Fully human IgG4 anti-PD-1 mAb**

**Sintilimab (Tyvyt; IIB308) (Innovent/Eli Lilly)** | Approved in China (HL) |
| Phase 3 in China: NSCLC, gastric cancer, nasopharyngeal carcinoma, CRC, esophageal SCC, HL, SCLC, HCC, rectal cancer |

**Zimberelimab (AB122, GLS-010) (WuXi Biologics/Harbin Gloria Pharmaceuticals/Arcus Biosciences)** | Phase 2 with US locations: NSCLC (ARC-7; NCT04262856), mCRC (ARC-6; NCT04381832) |
| Phase 2 in China: cervical cancer, HL |

**Subcutaneously administered PD-L1 nanobody**

**Enavesilimab (KN035) (3D Medicines/Alphamab Oncology/Simcere)** | Phase 3 in China: biliary tract cancer |

**Fully human IgG1 PD-L1 mAb**

**Cosibelimab (CK-301) (Checkpoint Therapeutics)** | Phase 1 in Australia, New Zealand, Poland, Russia, and Thailand: advanced cancers |

**MGG013 (Zai Lab/MacroGenics)** | Phase 3 with US locations: HER2-positive gastric/GEJ cancer (MAHOGANY; NCT04082364) |

**Bifunctional fusion protein; TGF-ßRII extracellular domains fused to human IgG1 PD-L1 mAb**

**Bintrufusp alfa (M7824) (EMD Serono)** | Phase 3 with US locations: biliary tract cancer (NCT04066491), SCLC (NCT03631706) |

**Bispecific targeting PD-L1 and CTLA-4**

**KN046 (Alphamab Oncology)** | Phase 2 in China: esophageal SCC, SCLC, TNBC |

**Small molecule inhibitor of VISTA, PD-L1, and PD-L2**

**CA-170 (Curis)** | Phase 1 with US locations: advanced solid tumors or lymphomas (NCT02812875) |

CRC, colorectal cancer; DART, dual-affinity retargeting; EOC, epithelial ovarian cancer; ES-SCLC, extensive-stage small cell lung cancer; GEI, gastroesophageal junction; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; HNSCC, head and neck squamous cell carcinoma; IgG, immunoglobulin G; mAb, monoclonal antibody; mCRC, metastatic castration-resistant prostate cancer; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; TGF, transforming growth factor; TNBC, triple-negative breast cancer.

*aTrials may be actively recruiting participants, not yet recruiting, or ongoing but not actively recruiting.
*bClinical trial is ongoing but not actively recruiting participants.
*cClinical trial is suspended because of coronavirus disease 2019 pandemic.
market worldwide, an increasing trend toward development of PD-1/PD-L1 inhibitors has recently surfaced among Chinese biotechnology companies. Several drugs are in clinical trials, and the NMPA has approved 4 in the past 18 months: camrelizumab (AilRuIKa), sintilimab (Tyvyt), toripalimab (Tuoyi), and, most recently, tislelizumab (BGB-A317).2,4

All these drugs are approved in China for Hodgkin lymphoma treatment. Additionally, toripalimab is approved for melanoma, and tislelizumab is indicated in metastatic urothelial carcinoma. Phase 3 trials in numerous indications are ongoing.

Beigene reported results at ASCO 2020 from an ongoing phase 3 trial of tislelizumab in combination with chemotherapy for the first-line treatment of advanced squamous NSCLC (NCT03594747); the study is being conducted at multiple sites in China. The addition of tislelizumab to paclitaxel and carboplatin (arm A) or to nab-paclitaxel (Abraxane) and carboplatin (arm B) improved PFS more than paclitaxel plus carboplatin. The median PFS in the 3 arms, respectively, was 7.6 months (HR, 0.52; P=.0001), 7.6 months (HR, 0.48; P<.0001), and 5.5 months. Serious TRAEs in the 3 arms were reported in 36.7%, 38.1%, and 24.8% of patients, respectively.10

Among the drugs in clinical development is envafolimab (KN035), a single-domain antibody (nanobody) against PD-L1 and the first PD-1/PD-L1 inhibitor to be developed as a subcutaneous formulation.46 Envafolimab showed promising safety and preliminary antitumor efficacy in patients with advanced solid tumors in phase 1 results presented at ASCO 2019.43 In a phase 2 study (NCT03667170), envafolimab demonstrated confirmed ORRs of 30% among 50 patients with MSH-H/dMMR advanced cancers, including colorectal and gastric cancers, according to interim findings reported at ASCO 2020. The ORR was 54.2% in the cohort of patients with colorectal cancer who had undergone prior chemotherapy.43

During a session titled “East Meets West: Chinese Pharma Explores Western Markets” held at the American Association for Cancer Research meeting in 2019, Richard Pazdur, MD, the director of the FDA’s Oncology Center of Excellence, urged Chinese companies to bring their PD-1/PD-L1 drugs to the US market in an effort to reduce prices.31

US and Chinese drug developers have already forged numerous collaborations. Beigene has entered into an agreement with Celgene to develop and commercialize tislelizumab for the treatment of solid tumors in all non-Asian countries and Japan, with Beigene retaining exclusive rights in Asian countries other than Japan.49 Innovent Biologics and Eli Lilly reached a similar partnership for sintilimab commercialization.33 Additionally, California-headquartered Arcus Biosciences licensed the PD-1 mAb zimberelimab (AB122, GLS-010) from WuXi Biologics and its partner Harbin Gloria Pharmaceuticals.35,36

**IN WITH THE NEW**

Companies are also seeking to improve efficacy by pursuing combination therapy, rather than monotherapy, right out of the gate. Besides chemotherapy and radiation therapy, the most popular additions to PD-1/PD-L1 inhibitors include VEGF inhibitors, other ICIs, and costimulatory receptor agonists.2

These strategies seek to overcome potential mechanisms of resistance to PD-1/PD-L1 inhibition and capitalize on synergistic antitumor activity. In addition to its role in angiogenesis, VEGF is thought to function in immune suppression.37 A host of other coinhibitory receptors exist, including CTLA-4 and LAG-3, against which mAbs are available. Meanwhile, agonists of costimulatory receptors, such as OX40, and their ligands have also been developed to boost T-cell activation.29

Manufacturers are also employing novel drug designs to capture combined mechanisms of action in a single molecule. Several bispecific antibodies and fusion proteins are in clinical development. These include bintrafusp alfa (M7824), a bifunctional fusion protein comprising tumor growth factor (TGF)-βRII extracellular domains linked to a PD-L1 mAb, that EMD Serono is developing.40

Cancer cells frequently express the cytokine ligand TGF-β, which exerts immunosuppressive effects that can hamper the efficacy of PD-1/ PD-L1 inhibitors.44 EMD Serono has advanced bintrafusp alfa into a head-to-head trial against pembrolizumab in the first-line treatment of PD-L1-positive NSCLC (NCT03631706).

Meanwhile, results from several expansion cohorts of an ongoing phase 1 trial of bintrafusp alfa (NCT02517398) have been reported at various recent conferences. Among 33 patients with heavily pretreated triple-negative breast cancer, 1 confirmed CR and 2 partial responses (PRs) were reported, and the median PFS and OS were 1.3 months and 7.8 months, respectively. Grade 3 TRAEs included anemia, asthenia, decreased appetite, rash, hypophysitis, and increased transaminases, with 1 death related to treatment.49

Among 25 patients in the cervical cancer expansion cohort, 6 confirmed responses (ORR, 24%) were reported, with 5 ongoing at data cutoff, as was an additional delayed PR. Grade 3 TRAEs occurred in 24% of patients, and 1 patient had grade 4 treatment-related hypokalemia. No deaths related to bintrafusp alfa treatment occurred.43

Finally, in 80 patients with chemotherapy-pretreated but immunotherapy-naïve advanced NSCLC, bintrafusp alfa therapy was associated with an ORR of 21.3% across the entire population, who had been treated with either 500 mg or 1200 mg every 2 weeks. Among patients who received the 1200-mg dose, the ORR was 36% (10 of 27 patients) in those with PD-L1-positive disease (21% expression) and 85.7% (6 of 7 patients) in those with high PD-L1 expression (on ≥80% of tumor cells). TRAEs occurred in 69% of patients, with grade 3 or higher TRAEs in 29%, and no treatment-related deaths were observed.44 In 2-year follow-up data reported at ASCO 2020, 18- and 24-month PFS and OS rates among those who received the 1200-mg dose were 18.4% and 11.0%, and 49.7% and 39.7%, respectively. At that dosage, the median OS was 21.7 months in those with PD-L1-positive tumors.45

Biotechnology companies are also pursuing small molecule inhibitors of PD-1/PD-L1, facilitated by publication of the crystal structure of the receptor-ligand complex in 2015.46 Small molecule inhibitors could overcome many of the limitations of mAbs, such as their poor penetration of solid tumors, inconvenient intravenous administration, daunting toxicity profiles, and costly production.16,17

Most of these drugs are still in preclinical development. However, Curis and its partner Aurigene are testing CA-170, a small molecule inhibitor of PD-L1, PD-L2, and the VISTA immune checkpoint protein, in a phase 1 trial in advanced solid tumors (NCT02812875), although questions about its ability to bind to PD-L1 have recently arisen.47
Important Safety Information on the following pages.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, and additional Important Safety Information on the following pages.
IN A PHASE 3 STUDY IN WHICH 94% OF PATIENTS WERE REFRACTORY TO REVLIMID*

**POMALYST + dex improved median survival vs high-dose dex**

**OVERALL SURVIVAL (ITT POPULATION, N=455)**

POMALYST + low-dose dex reduced risk of death vs high-dose dex

Median OS: **12.4 months** (95% CI 10.4, 15.3)

vs **8.0 months** (95% CI 6.9, 9.0)

(HR 0.70; 95% CI 0.54, 0.92; \( P=0.009 \))

OS Data cutoff: March 1, 2013.

POMALYST + low-dose dex doubled the median PFS of high-dose dex (primary endpoint):

3.6 months (95% CI 3.0, 4.6) vs 1.8 months (95% CI 1.6, 2.1) (HR 0.45; 95% CI 0.35, 0.59; \( P<0.001 \))\(^{1,2} \)

\(^*\)In the study, 94% of patients were refractory to REVLIMID, 79% of patients were refractory to bortezomib, and 74% were refractory to both REVLIMID and bortezomib.

\(^{1}\)In the Phase 3 trial, PFS and OS were based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final PFS and OS analyses.

\(^{2}\)PFS Data cutoff: September 7, 2012.

**Trial Design:** POMALYST was studied in a Phase 3, multicenter, randomized, open-label trial of POMALYST + low-dose dex vs high-dose dex in patients with relapsed/refractory multiple myeloma who had received at least 2 prior treatment regimens, including REVLIMID and bortezomib, and demonstrated disease progression on or within 60 days from the last therapy (ITT population, N=455). Some key exclusion criteria included serum bilirubin >2.0 mg/dL, AST/ALT >3x ULN, and CrCl <45 mL/min.\(^1,2\)

Patients in the POMALYST + low-dose dex arm (n=302) received 4 mg of POMALYST orally on Days 1-21 of 28-day cycles with 40 mg of low-dose dex once daily on Days 1, 8, 15, and 22 of 28-day cycles. Patients in the high-dose dex arm (n=153) received 40 mg of dex once daily on Days 1-4, 9-12, and 17-20 of 28-day cycles. Patients >75 years received 20 mg of dex in the same respective dosing schedules. Patients receiving POMALYST + low-dose dex were required to receive prophylaxis or anti-thrombotic treatment, as well as any other patient with a history of DVT or PE. The primary endpoint was PFS, and a key secondary efficacy endpoint was OS. Treatment continued until disease progression.\(^{1,2} \)

POMALYST + dex was studied in a variety of patients including\(^{1,3} \):

- Renal impairment\(^6\)
- Hepatic impairment\(^6\)
- Cytogenetic abnormalities\(^1\)
- Different risk classifications\(^5\)
- Varying ages\(^8\)

\(^*\)Patients in the POMALYST + dex study were excluded with CrCl <45 mL/min (according to the Cockroft-Gault formula or 24-hour urine collection); total bilirubin >34.2 μmol/L; and liver enzyme concentrations >3x ULN.

\(^{1}\)In the POMALYST + dex study, 41% of patients had del13q14, del17p13, t(4;14), or t(14;16).

\(^{2}\)The POMALYST + dex study included a variety of risk classifications, such as ECOG performance status and ISS staging. ECOG status was 0 in 32%, 1 in 49%, 2 in 17%, and 3 in <1% of patients; ISS Stage was I-II in 64%, and III in 32% of patients.

\(^{3}\)Median age of patients in the POMALYST + dex study was 64 years (range: 35-87).

Support your broad range of patients with multiple myeloma who have received REVLIMID and a PI—learn about the doublet and multiple triplet regimens with POMALYST at POMALYSTHCP.com/learn
Important Safety Information (continued)

**CONTRAINDICATIONS**

- **Pregnancy:** POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If POMALYST 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.

- **Hypersensitivity:** POMALYST is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, anaphylaxis) to pomalidomide or any of the excipients.

**WARNINGS AND PRECAUTIONS**

- **Embryo-Fetal Toxicity & Females of Reproductive Potential: See Boxed WARNINGS**
  - **Males:** Pomalidomide 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 POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm.
  - **Blood Donation:** Patients must not donate blood during treatment with POMALYST and for 4 weeks following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

- **POMALYST REMS® Program: See Boxed WARNINGS**
  - Prescribers and pharmacies must be certified with the POMALYST REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive POMALYST. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.
  - Further information about the POMALYST REMS program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

- **Venous and Arterial Thromboembolism:** See Boxed WARNINGS. 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). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors.

- **Increased Mortality With Pembrolizumab:** In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma 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.

- **Hematologic Toxicity:** Neutropenia (46%) was the most frequently reported Grade 3/4 adverse reaction in patients taking POMALYST in clinical trials, followed by anemia and thrombocytopenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.

- **Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST 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. DRESS 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 reactions can be fatal. Consider POMALYST interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue POMALYST for Grade 4 rash, exfoliative or bullous rash, or any other severe cutaneous reactions such as SJS, TEN or DRESS.

- **Dizziness and Confusional State:** In patients taking POMALYST in clinical trials, 14% experienced dizziness (1% Grade 3 or 4) and 7% a confusional state (3% Grade 3 or 4). Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

- **Neuropathy:** In patients taking POMALYST in clinical trials, 18% experienced neuropathy (2% Grade 3 in one trial) and 12% peripheral neuropathy.

- **Second Primary Malignancies:** Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.
Important Safety Information (continued)

• **Tumor Lysis Syndrome (TLS):** TLS may occur in patients treated with POMALYST. Patients at risk are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

• **Hypersensitivity:** Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to POMALYST have been reported. Permanently discontinue POMALYST for angioedema or anaphylaxis.

**ADVERSE REACTIONS**

The most common adverse reactions for POMALYST (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia.

In the phase III trial, nearly all patients treated with POMALYST + low-dose dex experienced at least one adverse reaction (99%). Adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥2% higher than control) included neutropenia (51.3%), fatigue and asthenia (46.7%), upper respiratory tract infection (31%), thrombocytopenia (29.7%), pyrexia (26.7%), dyspnea (25.3%), diarrhea (22%), constipation (21.7%), back pain (19.7%), cough (20%), pneumonia (19.3%), bone pain (18%), edema peripheral (17.3%), peripheral neuropathy (17.3%), muscle spasms (15.3%), and nausea (15%). Grade 3 or 4 adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥1% higher than control) included neutropenia (48.3%), thrombocytopenia (22%), and pneumonia (15%).

**DRUG INTERACTIONS**

Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALYST dose by 50%.

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** See Boxed WARNINGS. If pregnancy occurs 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 POMALYST pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy as well as female partners of male patients who are exposed to POMALYST. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALYST 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 pomalidomide in human milk, the effects of POMALYST on the breastfed child, or the effects of POMALYST on milk production. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in a breastfed child from POMALYST, advise women not to breastfeed during treatment with POMALYST.

- **Pediatric Use:** Safety and effectiveness have not been established in pediatric patients.

- **Geriatric Use:** No dosage adjustment is required for POMALYST based on age. Patients >65 years of age were more likely than patients ≤65 years of age to experience pneumonia.

- **Renal Impairment:** Reduce POMALYST dose by 25% in patients with severe renal impairment requiring dialysis. Take dose of POMALYST following hemodialysis on hemodialysis days.

- **Hepatic Impairment:** Reduce POMALYST dose by 25% in patients with mild to moderate hepatic impairment and 50% in patients with severe hepatic impairment.

- **Smoking Tobacco:** Advise patients that smoking may reduce the efficacy of POMALYST. Cigarette smoking reduces the AUC of pomalidomide by 32% by CYP1A2 induction.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, on the following pages.

References:
Dose Modification

Females of reproductive potential must have negative pregnancy tests before starting POMALYST treatment. POMALYST is contraindicated in pregnancy. Females of reproductive potential must use contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment (see Contraindications [4], Warnings and Precautions [5.1] and Use in Specific Populations [8.1, 8.3]). POMALYST is available through a restricted distribution program called POMALYST REMS (see Warnings and Precautions [5.2]).

1.1 Multiple Myeloma

POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Multiagent Therapy

The suggested multiagent therapy for patients with multiple myeloma is as follows:

- Pomalidomide: 4 mg once daily orally on Days 1-21 of repeated cycles (8.2).
- Dexamethasone: 4 mg once daily orally on Days 1-21 of repeated cycles (8.2).
- Thalidomide: 100 mg daily.

The multiagent therapy is administered with POMALYST (see Warnings and Precautions [5.1] and Use in Specific Populations [8.1, 8.3]).

2.2 Recommended Dosage for Patients with Severe Renal Impairment on Hemodialysis

For patients with severe renal impairment requiring dialysis, the recommended starting dose is 3 mg daily (25% dose reduction). Take POMALYST after completion of dialysis procedure on hemodialysis days (see Use in Specific Populations [8.6]).

2.3 Recommended Dosage for Patients with Hepatic Impairment

For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction) (see Use in Specific Populations [8.7]).

2.4 Recommended Dosage for Patients with Severe Venous and Arterial Thromboembolism

Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors (see Warnings and Precautions [5.3]).

2.5 Recommended Dosage for Patients with Hepatic Impairment

For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction) (see Use in Specific Populations [8.7]).

4 CONTRAINDICATIONS

4.1 Pregnancy

POMALYST is contraindicated in females who are pregnant. POMALYST can cause fetal harm when administered to a pregnant female (see Warnings and Precautions [5.1] and Use in Specific Populations [8.1]). Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis. 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.

4.2 Hypersensitivity

POMALYST is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., anaphylaxis, angioedema) to pomalidomide or any of the excipients (see Warnings and Precautions [5.7], Description [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death (see Use in Specific Populations [8.1]). POMALYST is only available through the POMALYST 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 POMALYST 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 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST 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 POMALYST 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]).

Blood Donation

Patients must not donate blood during treatment with POMALYST 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 POMALYST.

5.2 POMALYST REMS® Program

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

Required components of the POMALYST REMS program include the following:

- Prescribers must be certified with the POMALYST 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 POMALYST REMS program, must only dispense to patients who are authorized to receive POMALYST and comply with REMS requirements.

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

5.3 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial
thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with POMALYST and low-dose dexamethasone. In Trial 2, where anticoagulant therapies were mandated, thromboembolic events occurred in 8.0% of patients treated with POMALYST and low-dose dexamethasone (Low-dose Dex), and 3.3% of patients treated with high-dose dexamethasone. Venous thromboembolic events (VTE) occurred in 4.7% of patients treated with POMALYST and Low-dose Dex, and 1.3% of patients treated with high-dose dexamethasone. Arterial thromboembolic events include terms for arterial thromboembolic events, cerebrovascular accidents, and ischemic heart disease. Arterial thromboembolic events occurred in 3.0% of patients treated with POMALYST and Low-dose Dex, and 1.3% of patients treated with high-dose dexamethasone.

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). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

5.4 Increased Mortality in Patients with Multiple Myeloma When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone

In two randomized clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is recommended outside of controlled clinical trials. In trials 1 and 2, patients treated with high-dose dexamethasone.

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Investigations: Blood creatinine increased (6%, 3%), Weight decreased (0%, 0%), Weight increased (12%, 0%); Psychiatric disorders: Anxiety (0%, 0%), Confusional state (6%, 3%), Insomnia (0%, 0%); Renal and urinary disorders: Renal failure (8%, 7%).

- *Regardless of attribution of relatedness to POMALYST.*

  - POMALYST alone arm includes all patients randomized to the POMALYST alone arm who took study drug. 81 of the 107 patients had dexamethasone added during the treatment period.
  - Serious adverse reactions were reported in at least 2% patients in any POMALYST treatment arm.
  - Data cutoff: 01 March 2013.

In Trial 2 of 450 patients who received POMALYST + Low-dose Dex (N=300) or High-dose Dex (N=150), at least one adverse reaction was reported in 95% of patients.

All Adverse Reactions ≥5% in POMALYST + Low-dose Dex arm and at least 2% points higher than the High-dose-Dex arm included:

- Blood and lymphatic system disorders: Neutropenia (51%, 21%), Thrombocytopenia (30%, 23%), Leukopenia (13%, 5%), Febrile neutropenia (9%, 0%);
- General disorders and administration site conditions: Fatigue and asthenia (47%, 43%), Pyrexia (27%, 23%), Edema peripheral (17%, 11%), Pain (4%, 2%);
- Infections and infestations: Upper respiratory tract infection (31%, 13%), Pneumonia (19%, 13%), Neutropenic sepsis (1%, 0%);
- Gastrointestinal disorders: Diarrhea (22%, 19%), Constipation (22%, 15%), Nausea (15%, 7%), Arthralgia (9%, 5%);
- Respiratory, thoracic, and mediastinal disorders: Bronchospasm (16%, 13%), Pain in extremity (7%, 6%);
- Nervous system disorders: Peripheral neuropathy (17%, 12%), Dizziness (12%, 9%);
- Headache (8%, 5%), Tachycardia (8%, 5%);
- Peripheral neuropathy (9%, 3%);
- Skin and subcutaneous tissue disorders: Rash (8%, 1%), Pruritus (7%, 3%), Hypokalemia (4%, 3%);
- Metabolism and nutrition disorders: Decreased appetite (1%, 1%);
- Skin and subcutaneous tissue disorders:
  - Rash (1%, 0%);
  - Pruritus (0%, 0%);
  - Hypokalemia (4%, 3%);
  - Rash (8%, 4%);
  - Pruritus (7%, 0%);
  - Rash (1%, 1%);
  - Rash (1%, 0%);
thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central, and peripheral) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg/day. Oner embryofetal toxicities included increased resorptions leading to decreased number of viable fetuses.

In rabbits, pomalidomide was administered orally to pregnant females at doses of 10 to 250 mg/kg/day. Additional cardiac malformations such as interventricular septal defect were seen at all doses with increases up to 250 mg/kg/day. Additional malformations observed at 250 mg/kg/day included anomalies in limbs (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digits) and associated skeletal malformations (missed metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent ibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs, and a reduced average for ossified tarsals. No maternal toxicity was observed at the low dose (10 mg/kg/day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately equal to that reported in humans at the recommended dose of 4 mg/day. Additional embryo-fetal toxicity included increased resorption. Following daily oral administration of pomalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma pomalidomide concentrations were approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta. **8.2 Lactation**

**Animal Data**

Following a single oral administration of pomalidomide to lactating mothers at 250 mg/kg/day, pomalidomide was transferred into milk, with milk concentrations approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta.

**8.3 Females and Males of Reproductive Potential**

**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 POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST 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**

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

**Infertility**

Based on findings in animals, female fertility may be compromised by treatment with POMALYST [see Nonclinical Toxicology (13.1)].

**8.4 Pediatric Use**

Safety and effectiveness have not been established in pediatric patients.

**8.5 Geriatric Use**

No dosage adjustment is required for POMALYST based on age. Of the total number of patients in clinical studies of POMALYST, 44% were aged older than 65 years, while 16% were aged 75 years or older. No differences in effectiveness were observed between these patients and younger patients. In these studies, patients older than 65 years were more likely than patients less than or equal to 65 years of age to experience pneumonia.

**8.6 Renal Impairment**

In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 38% and the rate of SAE increased by 64% relative to patients with normal renal function; therefore, starting dose adjustment is recommended. For patients with severe renal impairment requiring dialysis, POMALYST should be administered after the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis [see Dosage and Administration (2.4)].

**8.7 Hepatic Impairment**

Pomalidomide is metabolized primarily by the liver. Following single dose administration, the AUC of pomalidomide increased 51%, 56%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic impairment [see Dosage and Administration (2.5)].

**8.8 Smoking Tobacco**

Cigarette smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction. Adverse effects of smoking may reduce the efficacy of pomalidomide.

**10 OVERDOSAGE**

Hemodialysis can remove pomalidomide from circulation.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of 12 monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes, and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. Drug-treated males in this study were mated with untreated females, all uterine parameters were comparable to controls. Based on these results, the observed effects were attributed to treatment of the females. **17 PATIENT COUNSELING INFORMATION**

Advised the patient to read the FDA-approved patient labeling (Medication Guide).
POMALYST REMS Program

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

- Patients must sign a Patient-Physician Agreement Form and comply with the requirements to receive POMALYST. 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)].
- POMALYST is available only from pharmacies that are certified in POMALYST REMS program. Provide patients with the telephone number and website for information on how to obtain the product.

Pregnancy Exposure Registry

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

Venous and Arterial Thromboembolism

Inform patients of the risk of developing 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 (5.3)].

Hematologic Toxicities

Inform patients on the risks of developing neutropenia, thrombocytopenia, and anemia and the need to report signs and symptoms associated with these events to their healthcare provider for further evaluation [see Warnings and Precautions (5.5)].

Hepatotoxicity

Inform patients on the risks of developing hepatotoxicity, including hepatic failure and death, and to report signs and symptoms associated with these events to their healthcare provider for evaluation [see Warnings and Precautions (5.6)].

Severe Cutaneous Reactions

Inform patients of the potential risk for severe skin reactions such as SJS, TEN and DRESS and to report any signs and symptoms associated with these reactions to their healthcare provider for evaluation [see Warnings and Precautions (5.7)].

Dizziness and Confusional State

Inform patients of the potential risk of dizziness and confusional state with the drug, to avoid situations where dizziness or confusional state may be a problem, and not to take other medications that may cause dizziness or confusional state without adequate medical advice [see Warnings and Precautions (5.8)].

Neuropathy

Inform patients of the risk of neuropathy and to report the signs and symptoms associated with these events to their healthcare provider for further evaluation [see Warnings and Precautions (5.9)].

Second Primary Malignancies

Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown [see Warnings and Precautions (5.10)].

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 (5.11)].

Hypersensitivity

Inform patients of the potential for severe hypersensitivity reactions such as angioedema and anaphylaxis to POMALYST. Instruct patients to contact their healthcare provider right away for any 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 (5.12)].
Experts Provide Tips on Harnessing MRD to Guide ALL Therapy

by CHRISTINA T. LOGUIDICE

Monitoring Minimal or Measurable residual disease (MRD) has proved a powerful risk-stratification tool in determining treatment for both pediatric and adult patients with acute lymphocytic leukemia (ALL). Defined as the presence of leukemic cells below the limit of detection on conventional morphology, MRD has demonstrated clinical impact as a prognostic factor in the management of ALL. Currently, MRD is used for assessing initial treatment response and subsequent definition of MRD-based risk groups with consequent risk stratification, monitoring disease burden in the setting of stem cell transplantation, and serving as an early marker of impending relapse. Novel therapies including bispecific T-cell engagers, monoclonal antibodies, and chimeric antigen receptor (CAR) T cells have recently advanced the treatment landscape.

During a recent OncLive Peer Exchange®, a panel of experts in adult and pediatric leukemia provided insight on how they use MRD to guide treatment decisions, including transplantation and choice of therapy in patients who demonstrate MRD positivity after induction and first- and subsequent-line therapies. They also offered an overview of blinatumomab (Blincyto), currently the only treatment approved for patients with ALL who have MRD-positive status in first or second complete hematologic remission, as well as other therapies that can be considered in patients with persistent MRD positivity, including inotuzumab ozogamicin (Besponsa) and CAR T-cell therapies.

Transplantation

Patients who remain persistently MRD positive pose a significant treatment challenge, and it is unclear whether additional approaches should be pursued to achieve MRD-negative status before these patients are taken to transplantation. “I don’t think there’s any straightforward approach, but for me, after 1 or 2 months of a treatment, if their MRD status is not changing, then those are the patients who we’ll just take to transplant,” panelist Jae Park, MD, said. He added that the decision also depends on the patient’s MRD level. “If it’s a low level, less than 0.01% or 0.1%, then you may consider those relatively lower levels of MRD to go to transplant. But with a high level of MRD, I may try a little bit more. It all depends on the condition of the patient, their previous lines of therapy, what additional therapeutic tools we have, and if there’s a reasonable chance I’m going to achieve that MRD negativity.”

On the pediatric side, panelist Rachel E. Rau, MD, said that she will try to do everything possible to get her patients to an MRD-negative status before transplantation because these patients have significantly improved outcomes. “Their chances of being cured are much greater if we can get them to that state,” she explained. She mentioned a study by Pulsipher and colleagues that found that even patients with MRD-positive status on next-generation sequencing (NGS), which is much more sensitive at detecting residual disease than its more commonly used counterpart, flow cytometry (FC), had inferior post-transplant outcomes, including a much higher risk of relapse and lower overall survival. Compared with FC, which can detect 1 cancer cell in 10,000 normal cells, NGS can detect 1 cancer cell in 1 million normal cells. In the study, NGS-MRD predicted relapse and survival more accurately than multichannel FC-MRD (P < 0.0001), especially in the MRD-negative cohort.

Participating in the panel are, from left, moderator Mark R. Litzow, MD, and Jae Park, MD.
Panelist Ryan D. Cassaday, MD, agreed that persistent MRD positivity is a challenging situation and explained that a careful balance is required. “Transplant is probably the only thing that’s going to be able to give that patient a chance of long-term remission, and we must always be mindful of the fact that these therapies we’re giving to try to achieve that level [of MRD negativity] may not work. It may make patients sicker. It may preclude them from moving ahead with the therapy that we’re ultimately trying to get them to,” he said, indicating there is a need for novel approaches to transplantation in this complex patient population.

**BLINATUMOMAB**

Blinatumomab is a first-in-class bispecific T-cell engager antibody against CR19/CD3. On March 29, 2018, the FDA granted blinatumomab accelerated approval as a treatment for adult and pediatric B-cell precursor (BCP)-ALL in first or second complete hematologic remission with an MRD of at least 0.1%. It was previously approved for the treatment of relapsed or refractory (R/R) BCP-ALL in adults and children.

Accelerated approval of blinatumomab in BCP-ALL patients with MRD-positive status was based on data from the open-label, single-arm BLAST trial (NCT01207388). The study included 113 evaluable patients aged 18 years or older who had received at least 3 chemotherapy blocks of standard ALL therapy and were in complete hematologic remission but had an MRD level of at least 0.1% using an assay with a minimum sensitivity of 0.01%. Patients received blinatumomab 15 µg/m² per day by continuous intravenous infusion for up to 4 cycles and could undergo allogeneic hematopoietic stem cell transplantation (HSCT) anytime after cycle 1. Of the 113 patients, 88 (78%) achieved a complete MRD response. In the subgroup of 110 patients with Philadelphia chromosome (Ph)-negative ALL in hematologic remission, the Kaplan-Meier estimate of relapse-free survival (RFS) at 18 months was 54%. Median overall survival (OS) was 36.5 months. In the landmark analyses, the RFS was 23.6 months in complete MRD responders and 5.7 months in MRD nonresponders (P = .002), and the OS was 38.9 months versus 12.5 months in these cohorts, respectively (P = .002). More recently, a 5-year follow-up analysis of the BLAST study showed a median OS of 36.5 months after blinatumomab treatment, with median OS not reached among the patients with a complete MRD response during cycle 1 of treatment. These data support the long-term efficacy of blinatumomab in adult patients with BCP-ALL and MRD-positive status.

BLAST is notable because it replicated the results of a smaller study, according to moderator Mark R. Litzow, MD. “[In the study] of 20 patients, 16 [80%] converted to MRD negativity,” he said. After a median follow-up of 33 months, the Kaplan-Meier estimate of hematologic RFS in this cohort was 61%. In a subgroup of 9 patients who received allogeneic HSCT after blinatumomab treatment, the hematologic RFS by Kaplan-Meier estimate was 65%. Of the subgroup of 6 Ph-negative MRD responders with no further therapy after blinatumomab, 4 were in ongoing hematologic and molecular remission at the time of the follow-up study’s publication, also suggesting good long-term efficacy with blinatumomab.

The panelists agreed that blinatumomab is usually the first agent they use in their adult and pediatric patients with BCP-ALL and MRD-positive status following standard chemotherapy because it is approved for this indication and has shown good safety and efficacy in these patients. In the BLAST trial, adverse events (AEs) were consistent with previous studies of blinatumomab. The most common severe AEs included neurologic events and cytokine release syndrome (CRS). Most neurologic events resolved, and even patients who experienced severe events were usually able to resume blinatumomab after the event resolved. Because patients in complete hematologic remission with MRD-positive status have a low disease burden, Litzow said CRS tends to be much milder in these patients than what is generally observed with blinatumomab in the R/R setting.

The panelists noted a few exceptions to the use of blinatumomab over other therapies in the MRD population. Rau said other treatments may be preferable in patients who may benefit from CD19-directed CAR T-cell therapy. “There’s some concern that blinatumomab may drive a CD19-negative situation, where it wouldn’t be amenable to CAR T,” she said. Cassaday said he would also be inclined to use a nonblinatumomab tactic in some Ph-positive patients. “For example, [if] I had started chemotherapy and imatinib and their...
response wasn’t very good but still relatively deep, I might continue the chemotherapy backbone but swap out the tyrosine kinase inhibitor for dasatinib [Sprycel],” he said.

**Emerging Data**

The panelists proceeded to discuss exciting emerging data for blinatumomab, along with some important trials that have the potential to better define and expand its use. Rau discussed the results of the Children’s Oncology Group phase 3 AALL1331 study, which was presented as a late-breaking abstract at the 2019 American Society of Hematology meeting.9

“I think we’re all very excited about the results of this trial, because it was a first relapse trial in which we took patients who were in their first relapse and defined them as high, intermediate, or low risk on the basis of timing of relapse, site of relapse, and then response to a 4-drug reinduction regimen. Patients who were high risk were defined as those who had an early relapse or didn’t achieve MRD less than 0.1%, and those patients were randomized post induction to either 2 blocks of blinatumomab or standard chemotherapy,” Rau said.

The AALL1331 study found blinatumomab to be superior to chemotherapy in both efficacy and safety, she said. Among patients with detectable MRD (≥0.01%) at the completion of block 1 of chemotherapy, the proportion that achieved undetectable MRD (<0.01%) after block 2 chemotherapy versus blinatumomab cycle 1 was 21% versus 79% (P<.0001).9 The tolerability of blinatumomab was also striking. “Very few patients on the blinatumomab arm had any substantial toxicity, whereas those on the standard chemotherapy arm, as you would predict, had higher rates of sepsis, febrile neutropenia, and some mortality due to therapy,” she said. As with the BLAST trial in adults, the pediatric patients treated with blinatumomab in the AALL1331 study had relatively low rates of CRS because most had a relatively low disease burden when the agent was introduced. As in adults, neurotoxic events were fairly common but fully resolved.

Based on the AALL1331 study data, Rau suggested that blinatumomab is a good bridge to transplant in high- and intermediate-risk relapsed patients. “[These] patients we still feel warrant transplant in second complete remission,” she said. The results for the low-risk arm of the trial have yet to be released. “For those patients, we replaced some of the intensive chemotherapy with blocks of blinatumomab versus just standard chemotherapy alone,” she said. “That is a population we think we can cure without stem cell transplant, so it will be really interesting to see if we were able to do that to a higher degree in patients treated with blinatumomab instead of just chemotherapy alone.”

Both Litzow and Rau said they are involved in studies assessing blinatumomab in the upfront setting. Litzow said his randomized phase 3 study (NCT02003222), which finished accruing patients in October 2019, is comparing combination chemotherapy with blinatumomab to see how well it works compared with induction chemotherapy alone in patients aged 30 to 70 years with BCP-ALL.8 Rau said the clinical trial (NCT03914625) she is conducting just opened in 2019 and will include a cohort of patients who are MRD positive by FC and a cohort who are MRD positive by NGS, both of which will be randomly assigned to chemotherapy either alone or with blinatumomab.15 This study also includes patients with Down syndrome, a population normally excluded from such trials. “Patients with Down syndrome have substantially higher rates of B-cell ALL,” Rau said. “They don’t respond well to our chemotherapy, so their outcomes are poor, and they don’t tolerate the therapies we give them either. They tend to really fall apart with our standard chemotherapy regimens. So, for our high-risk patients with Down syndrome, we’re going to nonrandomly assign them to chemotherapy arms in which we replace some of the intensive and toxic elements of therapy with courses of blinatumomab.”

**INOTUZUMAB OZOGAMICIN**

Inotuzumab ozogamicin combines a humanized CD22 monoclonal antibody with the cytotoxic agent calicheamicin. CD22 is expressed on leukemic blasts in more than 90% of patients with ALL.12 On August 17, 2017, it was approved by the FDA for the treatment of adults with R/R BCP-ALL.15 Unlike blinatumomab, it is not approved for patients with BCP-ALL in first or second complete hematologic remission and MRD-positive status.

“Blinatumomab is usually our first choice to get to MRD negativity for patients with B-cell ALL, [but] if they’re persistently positive, inotuzumab might be a consideration, especially if they received a multiagent chemotherapy and asparaginase-based chemotherapy, as well, [because] then we don’t really have a lot of other chemotherapeutic options,” Park said. He indicated that it would be reasonable to use inotuzumab ozogamicin alone or in combination with immunochemotherapy in this setting.

Park said there is a growing body of data regarding inotuzumab ozogamicin in the MRD setting. “Most of the data are coming from the morphologic relapse, salvage 1, and salvage 2 settings and in the later lines of relapse,” he said. The panelists did not discuss any of these data during the Peer Exchange; however, one such study, the phase 3 INO-VATE trial (NCT01564784), showed that patients with complete hematologic remission who achieved MRD-negative status had improved survival compared with MRD-positive patients, with the greatest survival benefit observed in those who achieved MRD-negative status during salvage 1 with inotuzumab ozogamicin.14 Overall, patients who proceeded to HSCT experienced the best outcomes.14 These findings are consistent with what has been observed with blinatumomab.

The panelists noted that a concern with inotuzumab ozogamicin is the risk of veno-occlusive disease (VOD). In the INO-VATE trial, VOD occurred in 23 of 164 patients (14%) treated with inotuzumab ozogamicin compared with 3 of 143 (2.1%) treated with standard-of-care chemotherapy.15 Park suggested a strategy for reducing the risk of this complication. “If you use inotuzumab to get to transplant, if you’re able to get to MRD negativity after 1, hopefully, or maybe even 2 cycles, and you’re not getting that much exposure to the inotuzumab, the risk for developing VOD could be minimized by avoiding the blood clotting agent and conditioning chemotherapy,” he said.

**CAR T-CELL THERAPY**

Currently, CAR T-cell therapy is approved
only for children, adolescents, and young adults (≤25 years) with R/R BCP-ALL; however, the panelists were hopeful that it will eventually be an option for older adults and suggested it may be ideally suited for the MRD-positive setting. “On the adult side, [CAR T-cell therapy] hasn’t really been tested in early-line settings just yet, although it’s been tested in the minimal disease setting,” Park said. “Some of our early trial data have shown that either way, with a couple different CAR T-cell therapies targeting CD19, the initial response rate is the same regardless of disease burden. You can have 80% bone marrow blast, or you can have 0.5% [very low-level disease], and you will get MRD negativity at the same rate, usually about 80% of the time.” He noted that the long-term outcome is better when patients receive CAR T-cell therapy when they have a lower disease burden.

Park also suggested that CAR T-cell therapy may be ideally suited for the persistent MRD setting. “If the persistently MRD-positive patients have received blinatumomab or some other agents, I think that would be a perfect setting where we should be studying the CAR T-cell therapy. That hasn’t been studied yet. I think it’s going to work very well in that setting, but again, we don’t have the data,” he said.

The panelists suggested that off-the-shelf CAR T-cell therapies may also have benefits in the MRD patients. “[These therapies] may overcome some of the limitations of T-cell quality, potency, or issues with patients, certainly for those patients who have had a lot of the chemotherapy. Because of immediate availability, it does make it possible to incorporate into the earlier-line setting, as opposed to waiting for collection and then somehow coming up with a way to maintain that MRD-negative state before you give the autologous CAR T therapy,” Park said. He noted that clinical trial data are needed to draw definitive conclusions.

**FUTURE OF MRD TESTING AND ALL MANAGEMENT**

Currently, in the United States, FC is the most-used modality to test for MRD, though more sensitive tools like NGS are already available and even more sensitive tools are on the horizon. “We’ll be able to pick up the smaller levels of a disease. The more challenging thing is what to do with that information. For that small disease, is it worthwhile to intensify or change the therapy that has been previously working or just continue with it? Hopefully, we can address these issues in large trials to really answer them, rather than borrowing the data piece meal,” Park said.

Another important consideration with current DNA-based MRD testing modalities, according to Cassaday: They do not provide information on patients’ CD19 or CD22 expression. “In the future, if we start using blinatumomab, CAR T-cell therapy, or inotuzumab ozogamicin in the frontline setting, we know that those agents can down-regulate expression of the targeted agents. So, if we are detecting at those superlow levels, but we don’t know anything about the immunophenotypic features, we may give them blinatumomab, but there’s no CD19 there to target. I think that’s going to be one thing that, as a field, we’re going to have to be cognizant of and sensitive to as not only the methods get better but [also] as these targeted agents get moved into therapy sooner,” he said.

In their concluding remarks, the panelists envisioned a future where patients with ALL will be spared from enduring countless invasive procedures and burdensome chemotherapy treatments. “I think of acute promyelocytic leukemia and how that was the worst prognostic acute leukemia 30 or 40 years ago, and now it’s the best prognosis and we’re not using chemotherapy. I think I see us moving in that direction in Ph-positive ALL, and I think with the Ph-like setting and some of these agents, we’re going to be in that direction, as well. I think the future is bright,” Litzow said.

**REFERENCES**

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HR: 0.69 95% CI 0.55–0.90; p = 0.002

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