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**Clinical perspectives presented by:**

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Vice Chair of the Malignant Hematology Department  
Moffitt Cancer Center  
Tampa, Florida  
United States

**David Steensma, MD**  
Hematologist Oncologist  
Novartis  
Cambridge, Massachusetts  
United States

**Uwe Platzbecker, MD**  
Hematologist Oncologist  
University Hospital  
Leipzig, Germany

**Andrew Wei, MBBS, PhD**  
Hematologist  
Alfred Hospital  
Melbourne, Australia

**Topics covered:**

**Expert Video 1:** Understand at a high level the link between TIM-3 expression and immune dysfunction in HR-MDS and AML.

**Expert Video 2:** Gain a deeper understanding about the role of immune dysfunction in HR-MDS, including how it manifests differently depending on disease severity.

**Expert Video 3:** Expand your knowledge about the role of TIM-3 as a driver of immune dysfunction and leukemic stem cell proliferation in HR-MDS.

**Expert Video 4:** Understand the key unmet needs in the HR-MDS space today, including poor prognosis and limited treatment options.

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The accelerated pathway has led to the approval of several immune checkpoint inhibitors across tumor types. However, a lack of benefit observed with the agents in confirmatory trials have resulted in increased scrutiny of the process.
Reevaluating the Accelerated Approval Pathway

AN EDITORIAL PUBLISHED IN the New England Journal of Medicine called attention to the recent troubles echoing across the immune checkpoint inhibitor (ICI) approvals. Despite the success in terms of the number of accelerated approvals granted to agents using the pathway, a trend of unconfirmed benefit in confirmatory trials has resulted in the removal of several indications for ICIs across tumor types.

Nearly half of the approvals for anti–PD-1/PD-L1 ICIs have been based on overall response rate and duration of response data from nonrandomized, single-arm trials. In March 2021, a spotlight was shined on the unconfirmed benefit with these agents in randomized trials when the FDA called for a hearing to discuss 10 dangling approvals, 9 of which used response rate as a primary end point. Since the announcement of the hearing, 6 indications have been withdrawn by manufacturers including 2 indications for atezolizumab (Tecentriq), 2 indications for nivolumab (Opdivo), and 1 indication each for pembrolizumab (Keytruda) and durvalumab (Imfinzi).

In an exclusive interview with OncologyLive®, Julia A. Beaver, MD, the chief of medical oncology in the FDA’s Oncology Center of Excellence and acting deputy director in the Office of Oncologic Diseases in the Center for Drug Evaluation and Research, discussed the future of approval pathways, specifically looking at lessons learned from immune checkpoint inhibitors.

“The intent is to use our learning from the checkpoint inhibitor class to apply the same regulatory standards to approve novel checkpoint inhibitors or indications that will benefit patients,” Beaver said. “Accelerated approval has been and will continue to be a very effective pathway for drug approval to bring promising therapies to patients years earlier. Even with the recent advisory committee meetings and withdrawals, there are still less than 10% of drugs approved under accelerated approval that have not verified benefit.” To read the full interview, see page 28.

As the status of ICIs and other approved agents reshape the treatment landscapes for patients with cancer, OncologyLive® remains dedicated to providing expert insights to translate the clinical news into practice. Programs including the OncLive Peer Exchange® and The Talk video programs feature panels of leading investigators contextualizing key data sets and how they will affect standards of care for your patients.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

REFERENCES

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Objectively Accurate Interpretation of Clinical Trials Results Poses a Challenge

by MAURIE MARKMAN, MD

MUCH HAS BEEN WRITTEN regarding the essential role of clinical trials in the major advances in cancer therapy and observed improvement in disease-related morbidity and mortality. The initiation of randomized trials comparing an existing standard of care with a proposed superior strategy has been a vital component in separating hypothesis and hype from objective and reasonably unbiased data.

However, it must be recognized that, to achieve this goal, it is necessary to pay attention to specific and essential components of the clinical trial process. These include, in the case of randomized studies, the selection of an appropriate control arm and trial sample size. Additionally, investigators should ensure treatment groups are well matched for recognized relevant prognostic factors (eg, age, tumor stage, prior therapy, and relevant comorbidities).

Unfortunately, despite great care in the development and conduct of trials in the oncology arena, one additional factor, in the opinion of this commentator, has not received adequate attention. This is the specific investigator (and/or sponsor) interpretation of the actual study results.

Concerns to be noted here may be relatively minor, such as the common use of quite subjective commentary to describe study findings. Examples include terms such as meaningful clinical activity with manageable safety, which may fall into this category.1 What is meaningful and manageable to one clinician or patient may not be viewed in this manner by others, especially when the objective data challenge this conclusion. At times, one may wonder whether the decision to use such ill-defined and possibly questionable terms in a manuscript submitted for peer review may not be that of the study investigators, but rather come directly from the sponsor or possibly a third-party communications group hired by a pharmaceutical company to provide writing/editorial assistance.

What is so difficult about simply concluding that “X% of patients in this study achieved a RECIST-defined response with a median duration of XX months (range, XX-XX),” that “XX% of patients experienced grade 3 or higher adverse effects (AEs), the most common of which were XXXX and XXXX,” or that “X% of patients required hospitalization for treatment-related AEs,” and letting readers decide for themselves whether the degree of clinical activity was meaningful and toxicity was manageable?

One may feel greater concern for the interpretation of certain objective data as positive outcomes. For example, in findings published in a recent report, a 7.9% response rate (n = 3 of 38) among patients with cervical cancer whose cancers did not express PD-L1 was suggested to provide a differential between the experimental checkpoint inhibitor being studied and another already on the market.1 Further examination of a larger patient population may confirm the utility of the agent in this clinical setting, or the duration of these uncommon responses may be particularly prolonged. However, this commentator feels compelled to ask whether we are now at a point in oncology where an objective response rate of less than 1 in 10 patients following treatment—with what will surely be an expensive anti-neoplastic drug—should be viewed as a positive finding.

“What is meaningful and manageable to one clinician or patient may not be viewed in this manner by others, especially when the objective data challenge this conclusion.”
A far more serious concern must be addressed regarding published data that appear to suffer from deficiencies of both scientific and, most disturbingly, basic ethical considerations. Unfortunately, recently reported data from a phase 3 trial exploring a novel anticancer agent in platinum-resistant ovarian cancer provide a disquieting example of this phenomenon. The trial highlighted here failed to reveal a statistically significant benefit for the experimental agent compared with the control regimen. However, this raises the question: How would the study results have been interpreted by the study investigators, various regulatory agencies/third-party payers, and, most important, treating oncologists and their patients if the data had revealed statistical superiority of this novel drug vs what is known today to be an inferior treatment approach in this clinical setting?

We now come to the final point; the ethical concern with the control arm in this trial, which called for PLD to be initially administered at a dose of 50 mg/m². Although initially FDA approved years ago for delivery at this dose level when employed as a single agent in platinum-resistant ovarian cancer, there are extensive data, including results of phase 3 randomized trials in this clinical setting, that reveal the essential therapeutic equivalence of a dose of 40 mg/m² and substantially reduced well-recognized symptomatic toxicity. Further, survey data reveal the drug is rarely administered in platinum-resistant ovarian cancer (4% of patients) in nonresearch, standard-of-care practice.

Therefore, the question to be asked of the study investigators and sponsor is: What was the justification for employing a PLD dose of 50 mg/m² when this potentially more toxic dose would infrequently be delivered to patients who were not participants in this research? Further, one must ask whether the institutional review boards responsible for ethical oversight of this study were aware of the status of current standard-of-care dosing of PLD, and if not, why not? Did the consent form for this study clearly state that the control arm dose of PLD was higher with the potential for more serious AEs than what the patient would likely receive if they did not participate in this study? Again, if not, why not?

Although it is not possible to know the thoughts of the peer reviewers and journal editors of this manuscript, it is reasonable to inquire whether they were aware of the concerns highlighted in this commentary.

REFERENCES


**Tebentafusp Is Cleared for Unresectable, Metastatic Uveal Melanoma**

The FDA has approved tebentafusp-tebn (Kimtrak) for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

The approval is based on efficacy data from the phase 3 IMCgp100-202 trial (NCT03070392), which showed the agent resulted in a significant benefit in overall survival (OS) vs investigator’s choice of treatment when used in the frontline setting (HR, 0.51; 95% CI, 0.37-0.71; P < .0001). Specifically, the estimated median OS was 21.7 months (95% CI, 18.6-28.6) in the investigative arm (n = 252) vs 16.0 months (95% CI, 9.7-18.4) in the control arm (n = 126), which included an investigator’s choice of treatment of single-agent pembrolizumab (Keytruda; n = 103), ipilimumab (Yervoy; n = 16), or dacarbazine (n = 7). The estimated 1-year OS rates in the tebentafusp and investigator’s choice arms were 73% (95% CI, 66%-79%) and 59% (95% CI, 48%-67%), respectively. The data cutoff date for the interim analysis was October 13, 2020, and the median duration of follow-up was 14.1 months.

The median progression-free survival was 3.3 months (95% CI, 3-5) vs 2.9 months (95% CI, 2.8-3.0) and the objective response rate was 9.1% (95% CI, 5.9%-13.4%) vs 4.8% (95% CI, 1.8%-10.1%) with tebentafusp vs investigator’s choice, respectively.

TO READ MORE, VISIT [bit.ly/34k1cJp](bit.ly/34k1cJp).

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**Idelalisib Indications for Relapsed Follicular Lymphoma, SLL Are Removed**

Gilead Sciences, Inc, voluntarily withdrew indications of idelalisib (Zydelig) for the treatment of patients with relapsed B-cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma (SLL) who had received at least 2 prior systemic therapies. Withdrawal of idelalisib from the US market for relapsed follicular lymphoma and SLL does not affect other idelalisib indications, including for patients with relapsed chronic lymphocytic leukemia.

In July 2014, the FDA granted an accelerated approval to the agent for use in combination with rituximab (Rituxan) based on findings from the phase 2 DELTA trial (NCT01284242). The continued approval was contingent upon providing evidence that supported confirmation of clinical benefit in follicular lymphoma and SLL. The company cited that the decision to withdraw these indications was because enrollment into the confirmatory study was an ongoing challenge with the evolving treatment landscape of these 2 diseases.

In DELTA, the agent elicited an independent review committee-assessed objective response rate (ORR) of 54% (95% CI, 42%-66%) in those with follicular lymphoma (n = 72), which included a complete response rate of 8% and a partial response (PR) rate of 46%. Among patients with SLL (n = 26), the ORR was 58% (95% CI, 37%-77%), all of which were PRs.


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**NDA Is Withdrawn for Parsaclisib Across Hematologic Indications**

Incyte withdrew the new drug application for parsaclisib for the treatment of patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma (MZL), and mantle cell lymphoma (MCL). The decision followed the company’s determination that confirmatory studies could not be completed within a period that would support the investment.

The application was supported by data from several phase 2 trials. Results from CITADEL-203 (NCT03126019) indicated parsaclisib elicited an objective response rate (ORR) of 75.4% per independent review committee (IRC) assessment in all treated patients with follicular lymphoma (n = 126).

In the daily dosing subset (n = 103), the ORR was 77.7%. In CITADEL-204 (NCT03144674), findings from cohort 2 (n = 100) showed parsaclisib produced an IRC-assessed ORR of 58.3% (95% CI, 46.1%-69.8%) in patients with MZL. In the daily-dosing subset (n = 72), the investigator-assessed ORR was 69.4%. As for CITADEL-205 (NCT03235544), the ORR was 68.5% (95% CI, 58.9%-77.1%) in all treated patients with MCL (n = 108). In the daily-dosing subset (n = 77), the ORR achieved was 70.1%.

TO READ MORE, VISIT [bit.ly/34kqpU3](bit.ly/34kqpU3).

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**Cemiplimab Will Not Move Forward for Advanced Cervical Cancer**

Regeneron Pharmaceuticals, Inc, and Sanofi voluntarily withdrew the supplemental biologics license application for cemiplimab-rwlc (Libtayo) as a second-line treatment for patients with advanced cervical cancer whose disease progressed on or after chemotherapy. The decision was made after the companies and the FDA were not able to align on certain postmarketing studies, according to a regulatory update issued in a news release.

In the 477 patients with squamous cell carcinoma, cemiplimab significantly improved the median OS vs chemotherapy at 11.1 months (95% CI, 9.2-13.4) and 8.8 months (95% CI, 7.6-9.8), respectively (HR, 0.73; 95% CI, 0.58-0.91; P = .00306). In the adenocarcinoma or adenosquamous carcinoma population (n = 131), the investigative arm demonstrated a median OS of 13.3 months (95% CI, 9.6-17.6) compared with 7.0 months (95% CI, 5.1-9.7) in the control arm (HR, 0.56; 95% CI, 0.36-0.85; P < .005).

TO READ MORE, VISIT [bit.ly/3IRFyLv](bit.ly/3IRFyLv).
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Insertion+ mNSCLC

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Mark A. Socinski, MD
Executive Medical Director
Member, Thoracic Oncology Program
AdventHealth Cancer Institute

Erminia Massarelli, MD, PhD, MS
Associate Professor
City of Hope Comprehensive Cancer Center

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- Explore EGFR Exon20 Insertion+ mNSCLC
- Review guideline-recommended testing
- Demonstrate how a new treatment option is designed for EGFR Exon20 insertion mutations
- Review the dosing safety and efficacy of a new treatment option

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THE FDA HAS APPROVED tebentafusp-tebn (Kimmtrak), the first available therapy for adult patients with HLA-A*02:01-positive unresectable or metastatic uveal melanoma.¹ The decision was supported by data from the IMCgp100-202 trial (NCT03070392), which showed that the agent resulted in a significant benefit in overall survival (OS) vs investigator’s choice of treatment, when used in the frontline setting (HR, 0.51; 95% CI, 0.37-0.71; P < .0001).

The estimated median OS in the investigative arm (n = 252) was 21.7 months (95% CI, 18.6-28.6) vs 16.0 months (95% CI, 9.7-18.4) in the control arm (n = 126). The estimated 1-year OS rates in the tebentafusp and investigator’s choice arms were 73% (95% CI, 66%-79%) and 59% (95% CI, 48%-67%), respectively. The OS benefit with tebentafusp was generally noted across the prespecified subsets examined in the trial.

ADDRESSING A DISTINCT OCULAR CANCER

Despite arising from melanocytes, uveal melanomas are genetically different from cutaneous and conjunctival melanoma. For example, up to 60% of cases of cutaneous melanoma present with a BRAF mutation, whereas approximately 90% of uveal melanoma present with GNA11 or GNAO mutations, which are also considered early events in the development of the disease.² Other distinctions include the distribution of immune cells and little is known about the microenvironment of metastatic uveal melanoma. Historically, patients with uveal melanoma have demonstrated nonsignificant responses to immune checkpoint inhibitors, and efforts to overcome this resistance resulted in the development of a bispecific protein that would engage the melanoma cells and simultaneously activate T cells.²,³

As investigators examined the agent in early studies, they observed that T-cell redirection was observed by cells that expressed both gp100 and HLA-A*02:01, narrowing the patient population of those who would benefit most with the novel agent.⁴

PIVOTAL TRIAL DESIGN AND OUTCOMES

The multicenter, randomized, phase 2 trial enrolled patients with local histologic or cytologic confirmation of metastatic uveal melanoma who were at least 18 years of age and had HLA-A*02:01 positivity, an ECOG performance status of 0 or 1, and at least 1 measurable lesion per RECIST 1.1 criteria.² Patients could not have been receiving systemic immunosuppressive treatment. They could not have received prior systemic or liver-directed therapy for metastatic disease, nor could they have had symptomatic central nervous system metastases or active autoimmune disease for which they were receiving glucocorticoids. Additionally, they could not have been receiving systemic immunosuppressive treatment.

A total of 378 participants were randomized 2:1 to receive tebentafusp or investigator’s choice of treatment, which included single-agent pembrolizumab (Keytruda; n = 103), ipilimumab (Yervoy; n = 16), or dacarbazine (n = 7). Because intrapatient dose escalation of tebentafusp had been found to reduce toxicity, investigators administered the drug intravenously (IV) at a dose of 20 μg on day 1, 30 μg on day 8, and 68 μg weekly thereafter. During the dose escalation, patients were monitored overnight after they received the treatment for the first 3 weeks.

Patients received treatment until radiographic progression, intolerable toxicity, investigator decision, or withdrawn consent. The exception was ipilimumab, which was administered for a maximum of 4 doses.

The primary end point of the trial was OS, and secondary endpoints included disease control rate, objective response rate, and progression-free survival (PFS). All secondary endpoints were evaluated via unblinded investigator assessment.

Among the randomized patients, 36% had an LDH level that was above the upper limit of normal and 5% had extraparetitic disease only; the median time since their primary diagnosis was 2.8 years. Investigators observed no substantial difference between the groups with regard to these variables. The data cutoff date for the trial’s interim analysis was October 13, 2020, and the median duration of follow-up was 14.1 months.

Additional data showed that tebentafusp also significantly improved PFS vs investigator’s choice of treatment in the intention-to-treat population. The median PFS was 3.3 months (95% CI, 3.0-5.0) with tebentafusp vs 2.9 months (95% CI, 2.8-3.0) with control therapy (HR, 0.73; 95% CI, 0.58-0.94; P < .01).² The 6-month PFS rates in the investigative and control arms were 31% and 19%, respectively.

Tebentafusp elicited an ORR of 9% (95% CI, 6%-13%) vs 5% (95% CI, 2%-10%) with investigator’s choice of treatment. The median duration of response in the investigative arm was 9.9 months vs 9.7 months in the control arm. Moreover, the disease control rate was higher with tebentafusp vs the control treatments, at 46% (95% CI, 39%-52%) vs 27% (95% CI, 20%-36%), respectively.

Findings from a landmark-based analysis revealed that tebentafusp also improved survival over investigator’s choice of treatment in those who experienced disease progression as their best response before day 100, at an estimated median OS of 15.3 months (95% CI, 12.0-not reached) vs 6.5 months (95% CI, 4.9-13.4), respectively (HR, 0.43; 95% CI, 0.27-0.68).

More patients who received tebentafusp experienced tumor regression that did not meet RECIST 1.1 criteria for partial response than those who received control treatment. In both arms, tumor regression was linked with longer OS.

Investigators reported that treatment-related adverse effects with tebentafusp were manageable and consistent with the proposed mechanism. The most common grade 3 or higher toxicities included rash (18%), pyrexia (4%), and pruritus (5%). Among the 245 patients who received tebentafusp, grade 3 cytokine release syndrome (CRS) was experienced by less than 1% of patients and was found to be generally well managed. Notably, no grade 4 or 5 CRS effects were reported. However, a box warning is included for this toxicity as it can become serious or life threatening if not appropriately managed.

“Uveal melanoma is a devastating disease that has historically resulted in death within a year of metastasis for our patients,” said John M. Kirkwood, MD, director of the Melanoma Center at the University of Pittsburgh Medical Center Hillman Cancer Center in Pennsylvania, in a news release.⁵ Kirkwood is also a professor of medicine, dermatology, and clinical and translational science at the University of Pittsburgh School of Medicine and the Clinical and Translational Science Institute at the University of Pittsburgh, and the 2017 Giants of Cancer Care® award winner in melanoma. “The approval of tebentafusp represents a major paradigm shift in the treatment of metastatic uveal melanoma, and for the first time offers hope to those with this aggressive form of cancer.”

REFERENCES

**BASELINE PATIENT CHARACTERISTICS**

**Median age (years, range)**

<table>
<thead>
<tr>
<th></th>
<th>Tebentafusp (n = 252)</th>
<th>Investigator’s choice (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>64</strong></td>
<td>(23-92)</td>
<td><strong>66</strong></td>
</tr>
</tbody>
</table>

**Largest metastatic lesion**

- **Tebentafusp**
  - ≤ 3.0 cm, stage M1a
  - 3.1-8.0 cm, stage M1b
  - ≥ 8.1 cm, stage M1c

- **Investigator’s choice**
  - ≤ 3.0 cm, stage M1a
  - 3.1-8.0 cm, stage M1b
  - ≥ 8.1 cm, stage M1c

**Median time since primary diagnosis**

- **3.0 years**
- **2.4 years**

**Location of metastasis**

- **Tebentafusp**
  - Hepatic only
  - Extrahepatic only
  - Hepatic and extrahepatic
  - Data missing

- **Investigator’s choice**
  - Hepatic only
  - Extrahepatic only
  - Hepatic and extrahepatic
  - Data missing

**COMMONLY REPORTED ADVERSE EFFECTS IN IMCgp100-202**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Tebentafusp (n = 245)</th>
<th>Investigator’s choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS (grade 3/4)</td>
<td>89%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Rash</td>
<td>83%</td>
<td>18%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>76%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>69%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>64%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>49%</td>
<td>2%</td>
</tr>
<tr>
<td>Chills</td>
<td>48%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>45%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Edema</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>39%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

**WARNINGS AND PRECAUTIONS**

- Skin reactions
- Elevated liver enzymes
- Embryo-fetal toxicity

Cytokine release syndrome (CRS) may be serious or life-threatening. Monitor patient for at least 16 hours following first 3 infusions of tebentafusp and then as clinically indicated.

**Mechanism of action**

- Tebentafusp is a bispecific gp100 peptide–human leukocyte antigen (HLA)-directed CD3 1-cell engager.
- Early study results demonstrated that HLA-A*02:01 expression on tumor cells increased the ability for gp100 protein recognition.

**Dose**

- 20 mcg on day 1
- 30 mcg on day 8
- 68 mcg on day 15
- 68 mcg once every week thereafter

**Company:** Immunocore Limited

**REFERENCES**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

The mechanism for the bleeding events is not well understood. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

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

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

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

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements.

Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,476 patients who received IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

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

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.
LIVING LONGER WITHOUT PROGRESSION

Superior PFS: IMBRUVICA® + rituximab vs FCR in E1912

89% (95% CI: 85, 92) estimated PFS rate with IMBRUVICA® + rituximab at 3 years vs 70% (95% CI: 61, 78) with FCR in patients ≤70 years old

HR=0.34 (95% CI: 0.22, 0.52; P<0.0001) (primary endpoint)

IMBRUVICA® (ibrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).

1L=frontline, CI=confidence interval, FCR=fludarabine, cyclophosphamide, and rituximab, HR=hazard ratio, PFS=progression-free survival.

Visit IMBRUVICAHCP.com to learn more

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

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

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS

The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions.

Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

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

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Dose modifications of IMBRUVICA® may be recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please see Brief Summary on the following pages.

IMBRUVICA® (ibrutinib) capsules, for oral use

INSTRUCTIONS AND USAGE

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with 17p deletion: IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (SLL) with 17p deletion.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hematologic: Fatal bleeding events have occurred in patients who received IMBRUVICA. Major hemorrhage (≥ Grade 3, serious, or central nervous system events; e.g., intracranial hemorrhage including subdural hematoma), gastrointestinal bleeding, hematoma, and post procedural hemorrhage occurred in 4% of patients, with fatal hemorrhage occurring in 0.4% of patients who received IMBRUVICA in 27 clinical trials. Bleeding events of any grade including bruising and petechiae occurred in 30%, and excluding bruising and petechiae occurred in 22% of patients who received IMBRUVICA, respectively. The mechanism for the bleeding is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA without anticoagulant or antiplatelet therapy experienced major hemorrhage. The addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without anticoagulant therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Clinical Studies (14) in Full Prescribing Information).

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA in clinical trials (see Adverse Reactions). Cases of progressive multifocal leukoencephalopathy (PML) and Pneumocystis jirovecii pneumonia (PJP) have occurred in patients treated with IMBRUVICA. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cytopenias: In 645 patients who received IMBRUVICA as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 3%, based on laboratory measurements. Monitor complete blood counts monthly.

Cardiac Arrhythmias and Cardiac Failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA. Grade 3 or greater ventricular tachycardia or tachyarrhythmia occurred in 0.2% of patients. Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4%, and Grade 3 or greater cardiac failure occurred in 1% of 1,478 patients who received IMBRUVICA in clinical trials. These events have occurred particularly in patients with a history of cardiac risk factors, heart failure, and acute infections, and a previous history of cardiac arrhythmia (see Adverse Reactions).

At baseline and throughout therapy, monitor patients clinically for cardiac arrhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmias (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias and cardiac failure appropriately, and if persistent, consider the risks and benefits of IMBRUVICA treatment and follow dose modification guidelines (see Dosage and Administration (2.2) in Full Prescribing Information).

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data as of January 12, 2016, of patients in the median time to onset was 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA as appropriate.

Secondary Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (4%), occurred among the 1,478 patients who received IMBRUVICA in clinical trials. The most frequent secondary primary malignancy was non-melanoma skin cancer (8%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the tumor burden risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Administration of Brutinib to pregnant rabbits and rats during periods of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those observed in women. Advise pregnant women of the potential risk to a fetus. Advise women who could become pregnant to avoid IMBRUVICA treatment. Advise men to use effective contraception during IMBRUVICA therapy (see Warnings and Precautions).

Study 1102: Adverse reactions and laboratory abnormalities from Study 1102 (N=51) using single agent IMBRUVICA 420 mg daily with a median duration of treatment of 16.5 months are presented in Tables 1 and 2.

Table 1: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with CLL/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruiting</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions | Fatigue | 33 | 0 |
| | Pyrexia | 24 | 2 |
| | Peripheral edema | 22 | 0 |
| | Anemia | 14 | 6 |
| | Chills | 7 | 0 |

Musculoskeletal and connective tissue disorders | Arthritis | 26 | 0 |
| | Muscle spasms | 18 | 2 |

Respiratory, thoracic and mediastinal disorders | Sputum | 22 | 0 |
| | Dyspnea | 14 | 0 |

Nervous system disorders | Headache | 18 | 2 |

Vascular disorders | Hypertension | 16 | 8 |

Metabolism and nutrition disorders | Decreased appetite | 16 | 2 |

Neoplasms benign, malignant, unspecified | Second malignancies | 10 | 2 |

* One patient death due to histiocytic sarcoma.

Table 2: Treatment-Emergent* Hematologic Laboratory Abnormalities in Patients with CL/L/SLL (N=51) in Study 1102

<table>
<thead>
<tr>
<th>Percent of Patients (N=51)</th>
<th>All Grades (%)</th>
<th>Grade 3 or (N=195)</th>
<th>Grade 3 or (N=195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets decreased</td>
<td>69</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>43</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CL/L/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthritis</td>
<td>24</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

Resonate: Adverse reactions and laboratory abnormalities described below in Tables 3 and 4 reflect exposure to IMBRUVICA with a median duration of 8.6 months and exposure to ofatumumab with a median of 5.3 months in RESONATE in patients with previously treated CLL/SLL.

Table 4: Adverse Reactions REPORTED in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CL/L/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>48</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>26</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Stomatitis*</td>
<td>17</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthritis</td>
<td>24</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>24</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Skin disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Contusion</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Eye disorders</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Table 4: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils decreased</td>
<td>57 (%)</td>
<td>26 (%)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>45 (%)</td>
<td>10 (%)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>21 (%)</td>
<td>0 (%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Ofatumumab (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>22 (%)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>16 (%)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>13 (%)</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsis</td>
<td>11 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain*</td>
<td>36 (%)</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>16 (%)</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>11 (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>30 (%)</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>19 (%)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>17 (%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>22 (%)</td>
</tr>
<tr>
<td></td>
<td>Gynaecia</td>
<td>10 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>21 (%)</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>19 (%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Dry eye</td>
<td>17 (%)</td>
</tr>
<tr>
<td></td>
<td>Lachrymation increased</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Vision blurred</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Visual acuity reduced</td>
<td>11 (%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>17 (%)</td>
</tr>
<tr>
<td></td>
<td>Skin infection*</td>
<td>15 (%)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia*</td>
<td>14 (%)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infections</td>
<td>10 (%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension*</td>
<td>14 (%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>11 (%)</td>
</tr>
<tr>
<td></td>
<td>Weight decreased</td>
<td>10 (%)</td>
</tr>
</tbody>
</table>

Subjects with multiple events for a given ADR term are counted once only for each ADR term.

Table 6: Treatment-Emergent Hematologic Laboratory Abnormalities in Patients with CLL/SLL in RESONATE-2

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Chlorambucil (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils decreased</td>
<td>57 (%)</td>
<td>26 (%)</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>45 (%)</td>
<td>10 (%)</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>21 (%)</td>
<td>0 (%)</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions Reported in at Least 10% of Patients and at Least 2% Greater in the IMBRUVICA Arm in Patients with CLL/SLL in HELIOS

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=195)</th>
<th>Placebo + BR (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia*</td>
<td>66 (%)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia*</td>
<td>34 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>36 (%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>12 (%)</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>20 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions</td>
<td>25 (%)</td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>11 (%)</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations</td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Skin infection*</td>
<td>10 (%)</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Hyperuricemia</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA (N=113)</th>
<th>Chlorambucil (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Neutropenia*</td>
<td>48 (%)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia*</td>
<td>36 (%)</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>17 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash*</td>
<td>36 (%)</td>
</tr>
<tr>
<td></td>
<td>Bruising*</td>
<td>32 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>34 (%)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>16 (%)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>12 (%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle spasms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular disorders</td>
<td>Hemorrhage*</td>
</tr>
<tr>
<td></td>
<td>Hypertension*</td>
<td>17 (%)</td>
</tr>
</tbody>
</table>

* Includes multiple ADR terms
† Includes 2 events of hemorrhage with fatal outcome in the IMBRUVICA arm and 1 event of neutropenia with a fatal outcome in the placebo + BR arm.
‡ Includes multiple ADR terms
‡‡ Includes multiple ADR terms
Table 8: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in ILLUMINATE (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Obinutuzumab (N=111)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>Grade 3 or Higher (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>General disorders</td>
<td>All Grades (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Upper respiratory tract infec.</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Skin infection</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Complement*</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

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

- * Includes multiple ADR terms
- † Includes one event with a fatal outcome.

**E1912: Adverse reactions described below in Table 9 reflect exposure to IMBRUVICA + rituximab with a median duration of 4.3 months and exposure to FCR with a median of 4.7 months in E1912 in patients who were previously untreated CLL/SLL who were 70 years or younger.

Table 9: Adverse Reactions Reported in at Least 15% of Patients in the IMBRUVICA Arm in Patients with CLL/SLL in E1912

<table>
<thead>
<tr>
<th>Body System</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>General disorders</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Severe neutropenia</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>61</td>
<td>5</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Gastrintestinal disorders</td>
<td>52</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>49</td>
<td>4</td>
</tr>
<tr>
<td>Bruising*</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Cough</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>16</td>
<td>1</td>
</tr>
</tbody>
</table>

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

- * Includes multiple ADR terms
- ** Includes one event with a fatal outcome.
PRC-07287

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Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased resorptions and post-implantation loss. The dose of 80 mg/kg/day in rats is approximately 14 times the exposure (AUC) in patients with MCL or marginal zone lymphoma (MZL) and 28 times the exposure in patients with CLL/SLL or Waldenström’s Macroglobulinemia (WM) administered the dose of 560 mg daily and 420 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in rats is approximately 6 times the exposure (AUC) in patients with MCL administering the dose of 560 mg daily.

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

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose.

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

Contraception: Females: IMBRUVICA can cause fetal harm when administered to pregnant women (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose.

Males: Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month following the last dose.

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

Geriatric Use: Of the 1,124 patients in clinical studies of IMBRUVICA, 64% were ≥ 65 years of age, while 23% were ≥75 years of age. No overall differences in effectiveness were observed between younger and older patients. Anemia (all grades), pneumonia (Grade 3 or higher), thrombocytopenia, hypertension, and atrial fibrillation occurred more frequently among older patients treated with IMBRUVICA.

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

Reduce the recommended dose when administering IMBRUVICA to patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Monitor patients more frequently for adverse reactions of IMBRUVICA (see Dosage and Administration (2.4), Clinical Pharmacology (12.3) in Full Prescribing Information).

Plasmapheresis: Management of hyperviscosity in WM patients may include plasmapheresis before and during treatment with IMBRUVICA. Modifications to IMBRUVICA dosing are not required.

PATIENT COUNSELING INFORMATION

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

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

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

- Cardiac arrhythmias and cardiac failure: Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema (see Warnings and Precautions).

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

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

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

- Embryo-fetal toxicity: Advise women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).

Advise females of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose (see Use in Specific Populations).

Advise males with female partners of reproductive potential to use effective contraception during treatment with IMBRUVICA and for 1 month after the last dose (see Use in Specific Populations, Nonclinical Toxicology (13.1) in Full Prescribing Information).

Lactation: Advise women not to breastfeed during treatment with IMBRUVICA and for 1 week after the last dose (see Use in Specific Populations).

Inform patients that they may experience loose stools or diarrhea and should contact their doctor if their diarrhea persists. Advise patients to maintain adequate hydration (see Adverse Reactions).

Active ingredient made in China.

Distributed and Marketed by: Pharmacyclics LLC
Sunnyvale, CA USA 94085

and Marketed by: Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent http://www.imbruvica.com

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Happy Upheavals Are Unveiled in Early-Stage Lung Cancer

by AMY L. CUMMINGS, MD

ALTHOUGH ADVANCES IN METASTATIC non-small cell lung cancer (NSCLC) treatment have dramatically affected cancer mortality, the translation of these approaches to earlier-stage NSCLC has just begun to bear fruit. The recent publications of the ADAURA (NCT02511106) and IMpower010 (NCT02486718) trials suggest that the incorporation of adjuvant targeted therapy and immunotherapy, respectively, may improve disease-free survival (DFS) following definitive surgery in selected populations with stage IB to IIA NSCLC. Although many questions remain, including whether DFS is an appropriate end point in earlier-stage NSCLC, early adopters have found the option of additional treatment researcing for patients with unfavorable features who are not willing or healthy enough to receive chemotherapy.

Fortunately, it is only going to get more complicated from here. CheckMate 816 (NCT02998528), which combines neoadjuvant nivolumab (Opdivo) with chemotherapy, and KEYNOTE-091 (NCT02504372), evaluating adjuvant pembrolizumab (Keytruda), have been reported as positive trials with the promise of upcoming survival data this year, and dozens of other neoadjuvant and adjuvant trials exploring permutations of drugs, timing, and biomarkers are ongoing. As we prepare to rethink how we manage earlier-stage NSCLC, a quick review of the history and unique features of neoadjuvant and adjuvant treatment may be helpful for context.

Platinum-based adjuvant chemotherapy changed standard-of-care practice in early-stage NSCLC approximately 15 years ago. Meta-analyses combining the results of JBR.10 (NCT00002583), ALPI, ANITA, IALT (NCT00002852), and BLT suggested that 4 to 6 cycles of platinum-based doublet chemotherapy lead to a 4% to 5% improvement in overall survival (OS) at 5 years in those with stage IB to IIA NSCLC, which is associated with a DFS hazard ratio of approximately 0.8. There are nuances regarding patient selection beyond the scope of this discussion—namely, whether the CALGB 9363 (NCT00002852) exploratory analysis that showed a benefit for stage IB patients with tumors greater than 4 cm should lead to a recommendation for adjuvant chemotherapy based on primary tumor size and whether all stage II patients should be offered adjuvant chemotherapy because the American Joint Committee on Cancer (AJCC) staging has changed since the original trials (ie, nearly all patients considered stage II in the 1990s to 2000s had N1 lymph node involvement, and AJCC stage IIA precludes lymph node involvement).

Conservatively, it is thought that for every 20 patients with lymph node involvement treated with adjuvant chemotherapy, 1 patient would have recurred and passed away from lung cancer in 5 years does not. A meta-analysis of platinum-based neoadjuvant chemotherapy trials including SWOG S9900 (NCT00004011), CHEST, NATCH (NCT00913705), and others showed an almost identical benefit, and receiving this chemotherapy treatment before or after surgery is considered acceptable.

The associated risks of neoadjuvant and adjuvant platinum-based chemotherapy include less than 1% treatment-associated death and approximately 50% hematologic toxicities, which represent the majority of high-grade complications. Approximately one-third of patients experience kidney dysfunction as a result of cisplatin and 5% endure some degree of permanent hearing loss. Salazar et al note that a significant proportion of patients with NSCLC start adjuvant chemotherapy outside of the recommended 8-to-12-week time frame following surgery, and receiving this chemotherapy treatment before or after surgery is considered acceptable. What we take from this history is that rapid drug development in this space is on point. Updated approaches to neoadjuvant and adjuvant treatment in early-stage NSCLC could have tremendous impact, and the use of consistently applied biomarkers beyond stage could be helpful for improved patient selection. Because waiting a decade or longer for survival end points can lead to challenges in application, it is appropriate to consider alternative end points, and many in our field are working on benchmarking these features. To date, an acceptable risk-benefit profile is profound benefit in few at the cost of limited toxicities in many, which may be reflected in the proportion of patients able to adhere to appropriately timed therapy.

Questions regarding how to select an optimal approach with conflicting biomarkers and what to do upon relapse, especially if combination therapy becomes standard of care, will be problems of tomorrow. Updating our routines to ensure molecular profiling and PD-L1 assessments are part of every NSCLC case and setting our own personal thresholds for acceptable risk-benefit may be the best way to prepare for the upheavals ahead.
## TABLE. Select Ongoing Neoadjuvant and Adjuvant Clinical Trials in Earlier-stage Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Trial name</th>
<th>ClinicalTrials.gov identifier</th>
<th>Stage/Timing</th>
<th>Treatment</th>
<th>Trial datesa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CheckMate 159</td>
<td>NCT02259621</td>
<td>I-IIIa, neoadjuvant</td>
<td>Nivolumab ± ipilimumab (Yervoy)</td>
<td>2014-2023</td>
</tr>
<tr>
<td>IMpower010</td>
<td>NCT02486718</td>
<td>IB-IIIa, adjuvant</td>
<td>Atezolizumab (Tecentriq)</td>
<td>2015-2022</td>
</tr>
<tr>
<td>KEYNOTE-091</td>
<td>NCT02504372</td>
<td>IB-IIIa</td>
<td>Pembrolizumab</td>
<td>2015-2024</td>
</tr>
<tr>
<td>ANVIL</td>
<td>NCT02595944</td>
<td>IB-IIIa, adjuvant</td>
<td>Nivolumab</td>
<td>2016-2024</td>
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<td>LCMC3</td>
<td>NCT0297301</td>
<td>IB-IIIb, neoadjuvant/adjuvant</td>
<td>Atezolizumab</td>
<td>2017-2025</td>
</tr>
<tr>
<td>PRINCEPS</td>
<td>NCT02994576</td>
<td>IB-IIIa, neoadjuvant</td>
<td>Atezolizumab</td>
<td>2016-2022</td>
</tr>
<tr>
<td>NEOSTAR</td>
<td>NCT03158129</td>
<td>I-IIIa, neoadjuvant</td>
<td>Nivolumab ± ipilimumab or chemotherapy</td>
<td>2017-2022</td>
</tr>
<tr>
<td>EMPOWER-CSCC-1</td>
<td>NCT03916627</td>
<td>I-IIIa, neoadjuvant</td>
<td>Ceripelimab</td>
<td>2019-2029</td>
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<tr>
<td>LUN0115</td>
<td>NCT04585477</td>
<td>I-III, adjuvant</td>
<td>Durvalumab</td>
<td>2021-2026</td>
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<td>AAAT0800</td>
<td>NCT04625699</td>
<td>II-IIIb, adjuvant</td>
<td>Durvalumab + tremelimumab</td>
<td>2021-2022</td>
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<tr>
<td>NeoCOAST-2</td>
<td>NCT05061550</td>
<td>II-IIIb, neoadjuvant/adjuvant</td>
<td>Durvalumab ± oleclumab + monalizumab</td>
<td>2021-2025</td>
</tr>
<tr>
<td><strong>Immunotherapy + chemotherapy</strong></td>
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</tr>
<tr>
<td>CheckMate 816</td>
<td>NCT02998528</td>
<td>IB-IIIa, neoadjuvant</td>
<td>Nivolumab + chemotherapy</td>
<td>2017-2028</td>
</tr>
<tr>
<td>KEYNOTE-671</td>
<td>NCT03425643</td>
<td>II-IIib, neoadjuvant/adjuvant</td>
<td>Pembrolizumab + platinum chemotherapy</td>
<td>2018-2026</td>
</tr>
<tr>
<td>IMpower030</td>
<td>NCT03456063</td>
<td>IB-IIa, neoadjuvant</td>
<td>Atezolizumab + platinum chemotherapy</td>
<td>2018-2026</td>
</tr>
<tr>
<td>AEGEAN</td>
<td>NCT03800134</td>
<td>II-III, neoadjuvant/adjuvant</td>
<td>Durvalumab + chemotherapy</td>
<td>2018-2024</td>
</tr>
<tr>
<td>IMpower132</td>
<td>NCT04367311</td>
<td>IB-IIIa, adjuvant</td>
<td>Atezolizumab + chemotherapy</td>
<td>2020-2024</td>
</tr>
<tr>
<td>MERMAID-1</td>
<td>NCT04385368</td>
<td>II-III, adjuvant</td>
<td>Durvalumab + chemotherapy</td>
<td>2020-2026</td>
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<tr>
<td>GO42501</td>
<td>NCT04832854</td>
<td>II-IIIb, neoadjuvant/adjuvant</td>
<td>Tiragolumab + atezolizumab ± chemotherapy</td>
<td>2021-2027</td>
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<tr>
<td><strong>Targeted therapy</strong></td>
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<tr>
<td>ADAURA</td>
<td>NCT02511106</td>
<td>IB-IIa, adjuvant</td>
<td>Osimertinib</td>
<td>2015-2023</td>
</tr>
<tr>
<td>BO40336</td>
<td>NCT03456076</td>
<td>IB-IIia, adjuvant</td>
<td>Alectinib ± chemotherapy</td>
<td>2018-2026</td>
</tr>
<tr>
<td>NAUTIKA1</td>
<td>NCT04302025</td>
<td>IIA-IIIb, neoadjuvant/adjuvant</td>
<td>Varied tyrosine kinase inhibitors</td>
<td>2020-2028</td>
</tr>
<tr>
<td>NeoADAURA</td>
<td>NCT04351555</td>
<td>II-IIIb, neoadjuvant</td>
<td>Osimertinib ± chemotherapy</td>
<td>2020-2029</td>
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<td>LIBRETO-432</td>
<td>NCT04819100</td>
<td>IB-IIa, adjuvant</td>
<td>Selpercatin</td>
<td>2021-2032</td>
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<td>Geometry-N</td>
<td>NCT04926383</td>
<td>IB-IIIA, neoadjuvant/adjuvant</td>
<td>Capmatinib</td>
<td>2021-2028</td>
</tr>
<tr>
<td></td>
<td>NCT05118854</td>
<td>IIA-IIIb, neoadjuvant</td>
<td>Sotorasib + chemotherapy</td>
<td>2022-2023</td>
</tr>
</tbody>
</table>

---

### REFERENCES

THE FIRST EVER TARGETED THERAPY FOR RESECTABLE EGFRm NSCLC

The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients\(^1\)\(^-\)\(^3\)

**PRIMARY ENDPOINT: DISEASE-FREE SURVIVAL IN PATIENTS WITH STAGE II/IIIA DISEASE (N=470)**

- 1-year DFS rate: 97%
- 2-year DFS rate: 90%
- 3-year DFS rate: 78%

**83% REDUCTION IN RISK of recurrence or death**

\(HR=0.17\) (95% CI: 0.12, 0.23), \(P=0.0001\)

Consistent results with or without prior adjuvant chemotherapy\(^2\)\(^4\)

- Patients in the ADAURA trial are treated with **ORAL TAGRISSO FOR 3 YEARS** or until disease recurrence or unacceptable toxicity\(^4\)

INDICATION

- TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

\(\text{Control arm}=\text{placebo.}\)

\(\text{Median DFS was not reached for TAGRISSO (95% CI: 58.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.}\)

\(\text{Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).}\)

\(\text{CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive;}\)

\(\text{HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable;}\)

\(\text{NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.}\)
BRIGHTER DAYS AHEAD FOR MORE EGFRm NSCLC PATIENTS

Your decision today impacts many tomorrows

REFER every resected NSCLC patient to a medical oncologist
TEST every surgical specimen for EGFR mutations
CHOOSE adjuvant TAGRISSO for every eligible patient

ADAURA study design: Phase III, double-blind, randomized, placebo-controlled trial in 682 patients with completely resected stage IB, II, and IIIA NSCLC with or without adjuvant chemotherapy. NSCLC patients had centrally confirmed EGFR mutations (exon 19 deletion or L858R mutation). Patients were stratified by stage (IB vs II vs IIIA), EGFR mutation (exon 19 deletion or L858R), and race (ASian vs non-Asian). Patients were randomized to either TAGRISSO (n=339, 80 mg orally, once daily) or placebo (n=343). The maximum interval between surgery and randomization was 26 weeks with adjuvant chemotherapy and 10 weeks without adjuvant chemotherapy. The primary endpoint of the study was DFS by investigator assessment in stage II/IIIA patients. The secondary endpoints were DFS in the overall population (stage IB/II/IIIA), DFS rate at 2, 3, 4, and 5 years, overall survival (stage II/IIIA and overall population), safety, and health-related QoL. The planned treatment duration was 5 years or until disease recurrence/unacceptable toxicity.1

OVERWHELMING EFFICACY

ADJUVANT TAGRISSO: DELIVERING
TAGRISSO demonstrated extraordinary disease-free survival FOR RESECTABLE EGFR m NSCLC
THE FIRST EVER TARGETED THERAPY

The first and only EGFR TKI to help prevent disease recurrence or death

• Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.1

† Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients; 0.3% of cases
• There are no contraindications for TAGRISSO

SELECT SAFETY INFORMATION

• Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a QTc >500 msec, and 3.1% of patients had an increase from baseline QTc >60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, as well as in patients on QT-modulating drugs. QTc interval prolongation has been reported in patients receiving TAGRISSO. Withhold TAGRISSO if QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

• Cardiomyopathy occurred in 3% of the 1479 TAGRISSO-treated patients. 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (5/325) of TAGRISSO-treated patients experienced LVEF decreases ≥10% from baseline and a drop to <50%. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO

• Keratitis was reported in 0.7% of 1479 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist

• Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed

• Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity

• Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose

• Most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue, and cough


Please see Brief Summary of Prescribing Information on adjacent pages.
INDICATIONS AND USAGE

WARNINGS AND PRECAUTIONS

Dosage Modifications

Adverse Reactions

Drug Interactions

QTc Interval Prolongation

Cardiovascular System

Auranofin, gold sodium thiomalate, and other gold-containing preparations, may cause QT prolongation.

Radiation-Induced Cardiomyopathy

Cutaneous Vasculitis

(m) is provided in the full Prescribing Information). If these conditions are not met, a patient should not be prescribed TAGRISSO.

Drugs that prolong the QTc interval (including Class I and III antiarrhythmic agents) can cause:

Constitutional (see Warnings and Precautions (5.3) and the full Prescribing Information)

Cutaneous findings with vomiting that develop subsequent to bleeding (see Warnings and Precautions (5.8) and the full Prescribing Information).

Table 1. Recommended Dosage Modifications for TAGRISSO

Table 2. Adverse Reactions Occurring in ≥25% of Patients Receiving TAGRISSO in ADJURA®

Dosing Adjustments

Clinical Trials

Adverse reactions noted in 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 data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1474 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials (AURA1 (n=279), AURA2 (n=279), and AURA3 (n=279)), and one dose-finding study (AURB (n=127)).

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ABDOMINAL PAIN, INTERSTITIAL LUNG DISEASE, AND HYPERSENSITIVITY REACTIONS

The most commonly laboratory abnormalities ≥20% of patients who received TAGRISSO were hyperglycemia (46%), proteinuria (39%), albuminuria (39%), hyperlipidemia (39%), and hypothyroidism (39%).

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Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADJURA®

Drug Interactions

Drug Interactions

Drug Interactions

Clinical Trials

Adverse Reactions

Acute Graft-Versus-Host Disease

Diabetes Mellitus

Clinical Trials

Clinical Trials

Clinical Trials

Clinical Trials

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Clinical Trials
Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (pemetrexed or erlotinib) (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Grade 3 or 4 (%)</td>
<td>Grade 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>59.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Nausea†</td>
<td>57</td>
<td>4.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>55.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Dry skin†</td>
<td>50</td>
<td>3.4</td>
</tr>
<tr>
<td>Itch†</td>
<td>35.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Pruritus†</td>
<td>17.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Nausea and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>21.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20.5</td>
<td>19.8</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry cough</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>0.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiovascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval†</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Intention and Infusion Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract infection</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality†</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (pemetrexed or erlotinib) (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Grade 3 or 4 (%)</td>
<td>Grade 3 or 4 (%)</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63.8</td>
<td>36</td>
</tr>
<tr>
<td>Anemia</td>
<td>35</td>
<td>0.4</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>16.6</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>5.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41.3</td>
<td>10</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>37</td>
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</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>30</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>22.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>22.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Increased ALP†</td>
<td>21.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Increased ALT†</td>
<td>16.6</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST†</td>
<td>14.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6. Adverse Reactions Occurring in >5% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
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</tr>
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<tr>
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<td></td>
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<tr>
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</tr>
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<tr>
<td>Intention and Infusion Disorders</td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract infection</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

<table>
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<tr>
<th>Laboratory Abnormality†</th>
<th>TAGRISSO (N=279)</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Increased AST†</td>
<td>14.0</td>
</tr>
</tbody>
</table>

*NCI CTCAE v4.0.
† Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO 279, Chemotherapy 133).
‡ Includes rash, rash generalized, rash maculopapular, rash papular, rash purpuric, rash vesicular, erythema, telangiectasia, acne, dermatitis, dermatitis herpetiformis, drug eruption, psoriasis, pustule.
§ Includes stomatitis and mouth ulceration.
¶ Includes fatigue, asthenia.
ǁ Includes rash, rash generalized, rash maculopapular, rash papular, rash purpuric, rash vesicular, erythema, telangiectasia, acne, dermatitis, dermatitis herpetiformis, drug eruption, psoriasis, pustule.
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AFTER 7 YEARS OF explosive growth, the development of PD-1/PD-L1 immune checkpoint inhibitor (ICI) therapy underwent a course correction last year, with the withdrawal of a range of indications due to study results that failed to reach thresholds for confirming clinical benefit. These withdrawals have had a muted impact on clinical practice so far, experts say, but that may change amid increasing scrutiny of the accelerated approval (AA) pathway that brought many of these drugs to patients.

Since 2014, the FDA has approved 7 ICIs, with more than 85 indications directed at the PD-1/PD-L1 immune checkpoint, and development is continuing with over 2000 clinical trials registered for testing existing and emerging agents in this drug class. The race to provide these therapies across a spectrum of cancer stages and settings has resulted in a “Wild West of drug development,” according to 2 high-ranking FDA officials. In a recent article in the New England Journal of Medicine, Julia A. Beaver, MD; and Richard Pazdur, MD, warned drug sponsors the FDA would no longer look favorably upon ICI approval applications based on single-arm clinical trials in patients with refractory disease. Pazdur, MD, warned drug sponsors the FDA would no longer look favorably upon ICI approval applications based on single-arm clinical trials in patients with refractory disease.

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Of 10 dangling approvals that were evaluated, 9 used ORR as a primary end point for AA. The manufacturers withdrew 6 of these indications, including 4 before the Oncologic Drugs Advisory Committee (ODAC) met in April 2021 to consider their future status. Another indication that received a negative ODAC vote is scheduled to be withdrawn, whereas 2 indications that had positive ODAC votes remain under discussion. Meanwhile, an indication for pembrolizumab (Keytruda) in urothelial carcinoma, which ODAC backed, subsequently was converted to a regular approval for a revised patient population based on overall survival data from a similar clinical trial (TABLE 1). Moving forward, regulators may be less likely to approve applications based on ORRs. “For the anti-PD-1/PD-L1 antibody class of drugs, where we were seeing low response rates and variable correlation to outcome, we will not be accepting low response rate single-arm trials to support [AA] for this class of drug,” Beaver wrote in an email interview with OncologyLive®. “For higher response rate trials with supportive duration, there is still a possibility of [AA].”

The agency is taking additional steps to improve the use of the AA pathway and other facets of cancer drug development, Beaver said. These efforts include Project Confirm, an OCE initiative that features searchable databases for oncology drugs approved through the AA pathway, including indications with verifiable clinical benefit and those that have been withdrawn. (For the full text of the interview, see the SIDEBAR). The project is intended to promote transparency about the AA pathway, Beaver said. The agency remains confident in the need for the AA process, which was introduced in 1992 to expedite drug development for patients with life-threatening unmet medical needs. “[AA] has been and will continue to be a very effective pathway for drug approval to bring promising therapies to patients years earlier,” Beaver said. “Even with the recent advisory committee meetings and withdrawals, there are still less than 10% of drugs approved under [AA] that have not verified benefit.”
CALLS FOR REFORMS

The agency’s efforts come at a time when the AA pathway has drawn increasing scrutiny in the oncology community. In April 2021, the Institute for Clinical and Economic Review (ICER) proposed several reforms, including stronger selection of surrogate end points, greater use of randomized controlled trials, and increased enforcement of requirements to complete confirmatory trials. Although FDA officials have cited the relatively small number of withdrawn indications as a sign of the program’s success, the ICER report questioned whether the standards for moving drugs to full approval require enough evidence and noted delays in conducting confirmatory studies.

More than 60% of the 278 applications granted under the AA program since its inception have been for oncology indications. Of 173 oncology AA indications, 89 (51%) have not been converted and 84 (49%) have been converted to full approvals, according to a Friends of Cancer Research dashboard. The median time elapsed since the AA was granted is 1.8 years for indications not yet converted, whereas the median time for the converted indications to reach full approval is 3.1 years. The site lists 17 withdrawn AA indications as of January 31, 2022, including the dangling requirements to complete confirmatory trials be initiated in a time of or after 2 or more therapies expressing PD-L1, with progression at time of or after 2 or more therapies expressing PD-L1, or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing PD-L1 or ineligible for any platinum-containing chemotherapy expressing 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ICI Therapy

premarket setting and making the withdrawal process “more nimble.”26 Overall, Allen sees the increased focus on the AA pathway as a positive development. “As science changes, it’s good to continually evaluate the policy that helps guide it, and that’s the source of some of these ongoing discussions,” he said. “Hopefully these discussions will help optimize these programs so they can best support the science coming in the future.”

TABLE 2. Other Oncology Indications Withdrawn After Accelerated Approvals4,14-19

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Accelerated approval indication</th>
<th>Date of accelerated approval</th>
<th>Date of withdrawal/ change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib (Copiktra)</td>
<td>Adult patients with relapsed or refractory FL after at least 2 prior systemic therapies</td>
<td>9/24/2018</td>
<td>12/17/2021</td>
</tr>
<tr>
<td>Ramiprilin (generic version)</td>
<td>PTCL in adults who have received at least 1 prior therapy</td>
<td>3/13/2020</td>
<td>12/8/2021</td>
</tr>
<tr>
<td>Romiprolin (Istodax)</td>
<td>PTCL in patients who have received at least 1 prior therapy</td>
<td>6/16/2011</td>
<td>7/30/2021</td>
</tr>
<tr>
<td>Olaratumab (Lartruvo)</td>
<td>In combination with doxorubicin for adults with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and that is not amenable to curative treatment with radiotherapy or surgery</td>
<td>10/19/2016</td>
<td>2/25/2020</td>
</tr>
<tr>
<td>Tositumomab and iodine 131 I (Bexxar)</td>
<td>Patients with relapsed/refractory low-grade follicular or transformed CD20+ NHL who have not received rituximab</td>
<td>12/22/2004</td>
<td>10/23/2013</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>To reduce the number of adenomatous colorectal polyps in patients with familial adenomatous polyposis as an adjunct to usual care</td>
<td>12/23/1999</td>
<td>6/6/2012</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>As monotherapy for locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemotherapy</td>
<td>5/5/2003</td>
<td>4/25/2012</td>
</tr>
<tr>
<td>Fludarabine phosphate (Ofortra)</td>
<td>For adults with B-cell CLL that has not responded to or progressed during or after treatment with at least 1 standard alkylating agent–containing regimen</td>
<td>12/18/2008</td>
<td>12/31/2011</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin (Mylotarg)</td>
<td>For patients with CD33+ AML in first relapse, 60 years or older, and not candidates for cytotoxic chemotherapy</td>
<td>5/17/2000</td>
<td>11/28/2011</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>In combination with paclitaxel for patients who have not received chemotherapy for metastatic HER2-negative breast cancer</td>
<td>2/22/2008</td>
<td>11/18/2011</td>
</tr>
<tr>
<td>Planned indication withdrawals (indications still on labels)</td>
<td></td>
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<tr>
<td>Idelalisib (Zydelig)</td>
<td>For patients with relapsed follicular B-cell NHL or relapsed SLL who have received at least 2 prior systemic therapies</td>
<td>7/23/2014</td>
<td>1/14/2022 (date of announcement)</td>
</tr>
<tr>
<td>Melphalan flufenamide (Pepaxto)</td>
<td>In combination with dexamethasone for relapsed/refractory multiple myeloma after at least 4 prior lines of therapy and with disease refractory to at least 1 proteasome inhibitor, 1 IMiD, and 1 CD38-directed monoclonal antibody</td>
<td>2/26/2021</td>
<td>10/22/2021 (date of announcement)</td>
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IMPLICATIONS FOR CLINICAL PRACTICE

Although ICIs have become an important facet of the oncology treatment landscape, the withdrawals of indications so far do not appear to be hampering clinical practice, particularly in tumor types with multiple approved ICIs. In urothelial carcinoma, ICI therapy has been “a bit of a roller coaster” since the novel agents were first approved in the malignancy, according to Matthew Galsky, MD, codirector of the Center of Excellence for Bladder Cancer and associate director for Translational Research, both at The Tisch Cancer Institute at Mount Sinai in New York, New York.

“Both atezolizumab (Tecentriq), a PD-L1 inhibitor, and pembrolizumab were approved under the AA pathway in 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy,21,22 Less than a year later, based on interim study data, the FDA limited both drugs in the frontline setting to cisplatin-ineligible patients whose tumors expressed PD-L1, or in those who are not eligible for any platinum-containing therapy regardless of PD-L1 status.4 After the ODAC hearing in April 2021, the FDA converted the pembrolizumab indication to a regular approval for patients who are not eligible for any platinum-containing therapy. The first-line indication for atezolizumab remains under discussion.1,9

Meanwhile, Genentech and AstraZeneca voluntarily withdrew AA indications for atezolizumab and durvalumab (Imfinzi), respectively, for patients with urothelial carcinoma that progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.5 Despite these changes, 4 ICIs retain indications in urothelial carcinoma (pembrolizumab, atezolizumab, nivolumab [Opdivo], and avelumab [Bavencio]).23-26 “There were so many of these PD-1 and PD-L1 inhibitors approved, at least in patients who had progressed despite prior chemotherapy, that the removal of 1 or 2 [indications] hasn’t had a clinical impact because there are still other drugs in that same class available,” Galsky said. At least part of 1 approval is retained in the frontline platinum-ineligible setting, he added.

“If there weren’t other drugs in the same class available, and there was the inability to prescribe these drugs at all, then that would take away a very important part of our
treatment armamentarium,” Galsky said. “These drugs are incredibly effective for a subset of patients and would have lost their approvals based on the consequences of the way the [AA] pathway is set up.”

Galsky, who was a leading investigator on the pivotal phase 2 IMvigor210 study (NCT02108652) into frontline atezolizumab monotherapy, said confirmatory trials are challenging to conduct. “They’re difficult to do in the exact same patient population because the drugs are already available. That certainly impacts whether patients would be willing to enrol on a study and investigator enthusiasm for enrolling patients on a study. Even if patients do [enroll], there’s the potential for contamination of the results as patients come off study and can get that treatment as standard care,” he said. “That created this complexity once you have the [AA]. How do you definitively prove the drugs work, because you can’t do it in the same patient population?”

Looking at AA indications from a broader scope, Galsky said the potential impact on clinical practice looms larger than immediate circumstances. “There is potentially an impact from the clinical science standpoint in that it makes us think about the consequences of the [AA] pathway as currently devised and the potential implications if we hadn’t had all those other drugs in the same class available—if this would have led to the inability to prescribe these drugs at all, to certain patient populations, which, based on the combination of data, are an important part of our treatment armamentarium,” he said.

In triple-negative breast cancer (TNBC), the changing ICI landscape also provides patients with other options. In August 2021, Genentech decided to voluntarily withdraw the AA indication for atezolizumab, even though the ODAC voted by a 7 to 2 margin to recommend the indication be retained pending additional trial data. Atezolizumab was approved through the AA pathway in March 2019 in combination with nab-paclitaxel (Abraxane) in patients with metastatic TNBC whose tumors express PD-L1, a decision that converted an AA indication from November 2020. Pembrolizumab also received a regular approval for high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, then continued as a single agent as adjuvant treatment after surgery.

Both approvals are based on findings from the phase 3 KEYNOTE-522 (NCT03036488) in which 1174 patients with newly diagnosed, previously untreated, high-risk, early-stage TNBC were randomized 2:1 to receive chemotherapy with pembrolizumab or placebo. The main efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). The pCR rate was 63% (95% CI, 59.5%-66.4%) for patients who received the pembrolizumab combination compared with 56% (95% CI, 50.6%-60.6%) for those in the placebo arm. The number of patients who experienced an EFS event was 123 (16%) and 93 (24%), respectively, in the pembrolizumab and placebo groups (HR, 0.63; 95% CI, 0.48-0.82; P = .00031).

The availability of pembrolizumab for this patient population provides an ICI option despite the withdrawal of the atezolizumab indication, noted Kevin Kalinsky, MD, MS, the Louisa and Rand Glenn Family Chair in Breast Cancer Research and director of Glenn Family Breast Center and Breast Medical Oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia.

Some patients would still be candidates for atezolizumab therapy because different assays are used to assess PD-L1 status for each drug. Atezolizumab was approved for patients with PD-L1-stained tumor-infiltrating immune cells covering greater than or equal to 1% of the tumor area. For pembrolizumab, PD-L1 positivity is defined as a combined positive score greater than or equal to 10. The Society for Immunotherapy of Cancer (SITC) guidelines recommend the VENTANA PD-L1 (SP142) assay be used for atezolizumab and the PD-L1 IHC 22C3 assay be used for pembrolizumab.

Although many patients meet the threshold for PD-L1 expression on both tests, atezolizumab remains an option for those who are positive on SP142 but not 22C3, said Kalinsky, who was a member of the SITC guidelines panel. “For those patients, there are communications that can happen directly with the company, as well as directly with insurance companies, to see [whether] there can be coverage to patients who were previously on atezolizumab and responding,” he said. “We’ve been able to continue that therapy. If there [are] any barriers, we speak to the insurance company and/or Genentech directly.”

For practicing oncologists sorting out revised rules for using ICIs, keeping up with the changes can be challenging. However, Galsky said there are indications that community oncologists can navigate the shifting landscape, at least in urothelial carcinoma. He noted research findings suggest practicing oncologists were able to adapt to changes in ICI therapy in 2018 after the FDA restricted atezolizumab and pembrolizumab use to patients with PD-L1-positive tumors.

“That analysis showed there was a dramatic change in the prescribing of frontline immune checkpoint blockade to patients who were eligible before and after the FDA label change, suggesting that yes, indeed, the community can keep up with these changes in the context of [AA], that the data do disseminate, and prescribing on label is pursued,” Galsky said, who participated in the study.
Taming the Wild West: the View From the FDA

ALTHOUGH PD-1/PD-L1 IMMUNE CHECKPOINT inhibitors have generated important treatment options for patients with many different tumor types, a hotly competitive drug development scene has resulted in an overabundance of clinical trials, often for redundant indications, an inefficient use of resources, and a lack of focus on earlier-stage disease, according to 2 leading FDA officials.

Julia A. Beaver, MD, and Richard Pazdur, MD, compared the environment to the Wild West in a recent article published in the New England Journal of Medicine. They called for greater collaboration among industry sponsors on diagnostics, regulatory submissions, and multinational clinical trials. Beaver is the chief of medical oncology in the FDA’s Oncology Center of Excellence (OCE) and acting deputy director in the Office of Oncologic Diseases in the Center for Drug Evaluation and Research. Pazdur, a 2019 Giants of Cancer Care® award winner for Community Outreach, is the director of the OCE.

In an email interview with OncologyLive®, Beaver responded to questions about several points raised in the article.

The article seems to declare the FDA will not view data from single-arm trials that use ORR as an end point as evidence for accelerated approval. Is this the direction the agency plans to take, or are there circumstances in which single-arm trials would still be considered? For the anti–PD-1/PD-L1 antibody class of drugs, where we were seeing low response rates and variable correlation to outcome, we will not be accepting low response rate single-arm trials to support accelerated approval for this class of drug. For higher response rate trials with supportive duration, there is still a possibility of accelerated approval.

We are also encouraging companies to conduct a randomized trial with coprimary end points of response rate and PFS/OS [progression-free survival/overall survival] so that the trial has the potential to support accelerated approval based on response rate followed by confirmation of benefit in the same trial with the longer-term outcome end points. We are recommending this approach, as it will also allow a drug to be developed for accelerated approval for an earlier line of therapy, thereby bringing potential benefit to a greater number of patients, and having the confirmatory trial embedded into the study will create a shorter time to confirmation.

Concerning clinical trials conducted outside the US, the article suggests studies conducted in a single country would not be adequate for supporting approvals in the United States. Is this a policy the FDA is pursuing now? In order to receive a US approval, trials conducted outside the US need to demonstrate applicability and generalizability of their results to the US population. With large multinational trials—the preferred approach—we have the opportunity to examine both safety and efficacy in various regions and countries to ensure consistency of results. There are greater challenges to determining applicability and generalizability when there is a trial conducted in a single ex-US [non-US] country, and the burden is on the company to demonstrate how this data can be extrapolated to the heterogeneous US population with its multiple ethnic and racial constituents and potentially different standards of care.

This article seems to signal we’re entering a more tightly regulated era for checkpoint inhibitor drugs. Is that the case? If not, how would you describe the FDA’s direction? We continue to apply the same standards to drug regulation, and as the science and our knowledge evolve, we are able to apply those standards in a more educated manner. For instance, as we gathered evidence on checkpoint inhibitors and saw low response rates for this class of drug as not being reflective of an end point reasonably likely to predict clinical benefit, we have adapted our approach to accelerated approval for this drug class.

What is the potential clinical impact of more tightly regulating oncology drug approvals on patients and on practicing oncologists? The intent is to use our learning from the checkpoint inhibitor class to apply the same regulatory standards to prove novel checkpoint inhibitors or indications that will benefit patients. Accelerated approval has been and will continue to be a very effective pathway for drug approval to bring promising therapies to patients years earlier. Even with the recent advisory committee meetings and withdrawals, there are still less than 10% of drugs approved under accelerated approval that have not verified benefit.

REFERENCES
Do you have a patient with relapsed/refractory adult B-cell acute lymphoblastic leukemia?

We are conducting the single arm, open-label, multi-center phase 2 FELIX study (NCT04404660) to evaluate the investigational CD19 CAR T-cell product called AUTO1 (obecabtagene autoleucel or obe-cel) in patients with relapsed/refractory adult B-cell acute lymphoblastic leukemia. The primary objective of the study is to evaluate the safety and efficacy of AUTO1 given as a split dose on day 1 and on day 10. Following the initial dose of AUTO1, patients will be observed closely for at least 10 days in hospital. Patients will then be in follow-up until the end of the study. We are seeking assistance from referral centers and those physicians who treat adult B-ALL patients in regional community hematology/oncology clinics to help us identify qualified study participants.

clinicaltrials@autolus.com

www.autolus.com
Trastuzumab Deruxtecan Upholds OS Improvement in HER2+ Advanced Gastric, GEJ Cancer

by GINA MAURO

FAM-TRASTUZUMAB DERUXTECAN-NXXI (ENHERTU) demonstrated a 40% reduction in the risk of death vs standard chemotherapy in patients with HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. Updated results of the DESTINY-Gastric01 trial were presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.1

The updated median overall survival (OS) with trastuzumab deruxtecan remained at 12.5 months (95% CI, 10.3-15.2) compared with 8.9 months (95% CI, 6.4-10.4) with chemotherapy (HR, 0.60; 95% CI, 0.42-0.86).

“With continued follow-up after the primary analysis, trastuzumab deruxtecan demonstrated a clinically meaningful OS benefit and clinically relevant improvement in objective response rate compared with standard chemotherapy in HER2-positive advanced gastric or GEJ cancer,” lead study author Kensei Yamaguchi, MD, said in a presentation of the data. Yamaguchi is managing director of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research in Tokyo, Japan.

In January 2021, the FDA approved trastuzumab deruxtecan for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a previous trastuzumab (Herceptin)-based regimen.2

The agency based their decision on primary findings from DESTINY-Gastric01 (NCT03329690), which showed that the median OS with trastuzumab deruxtecan was 12.5 months (95% CI, 9.6-14.3) compared with 8.4 months (95% CI, 6.9-10.7) with irinotecan or paclitaxel in this patient population (HR, 0.59; 95% CI, 0.39-0.88; P = .0097).3

DESTINY-Gastric01 is an open-label, multicenter, randomized, phase 2 study. Investigators evaluated trastuzumab deruxtecan vs physician’s choice of standard chemotherapy in patients with HER2-expressing advanced gastric or GEJ adenocarcinoma who had received at least 2 prior regimens, including fluoropyrimidine, a platinum-based agent, and trastuzumab or an approved biosimilar. Patients who had or were suspected to have interstitial lung disease (ILD) or pneumonitis, or a history of noninfectious ILD or pneumonitis that had been treated with steroids, were excluded from enrollment.

A total of 188 patients were randomized 2:1 to receive either trastuzumab deruxtecan at 6.4 mg/kg every 3 weeks (n = 125) or chemotherapy with irinotecan or paclitaxel (n = 62). Eighty-six percent of participants had received a prior taxane, 71% had received ramucirumab (Cyramza), and 31% had received prior PD-1/PD-L1 inhibitors. Stratification factors included country, ECOG performance status, and HER2 status.

The median age was 65.5 years (range, 28-82), and most patients were from Japan (79.9%). Forty-nine percent of patients had an ECOG performance status of 0, and patients either had intestinal histology (66.3%), diffuse histology (25.7%), or other (8.1%). Most patients (76.3%) had IHC 3+, IHC 2+, or ISH+ HER2 expression and most patients (87.6%) also had gastric or GEJ as their primary cancer site. Patients had tumors measuring less than 5 cm (50.4%), between 5 and 10 cm (28%), or at least 10 cm (16.8%); measurements were not reported for 4.8% of patients.

Additionally, patients had received either 2 (57.1%), 3 (28.1%), or at least 4 (14.9%) prior lines of systemic therapy, which included trastuzumab (100%), ramucirumab (70.7%), taxane (86.4%), irinotecan or another topoisomerase I inhibitor (7.3%), or an immune checkpoint inhibitor (31.3%). Patients in the trastuzumab deruxtecan group were more than twice as likely to have received 4 or more prior lines of therapy as patients in the chemotherapy group (20.0% vs 9.7%, respectively).4

The primary end point of the trial was objective response rate (ORR) per independent central review (ICR). Secondary end points comprised OS, duration of response (DOR), progression-free survival, confirmed ORR, and safety. The data cutoff date for OS was June 3, 2020, after a median follow-up of 18.5 months.
The median time to response was similar between the trastuzumab deruxtecan and chemotherapy arms, at 1.5 months (95% CI, 1.4-1.7) with trastuzumab deruxtecan and 1.6 months (95% CI, 1.3-1.7) with chemotherapy (TABLE). These data show that most patients who received trastuzumab deruxtecan had a reduction in tumor size compared with approximately half of patients receiving chemotherapy,” Yamaguchi said.

Regarding safety, grade 3 or higher adverse events (AEs) occurred in 85.6% of patients who received trastuzumab deruxtecan compared with 56.5% of those who received chemotherapy. The most common grade 3 or higher AEs were decreased neutrophil count (51.2% vs 24.2%, respectively), anemia (38.4% vs 22.6%), and decreased white blood cell count (20.8% vs 11.3%). Sixteen patients (12.8%) experienced ILD or pneumonitis related to trastuzumab deruxtecan, as determined by an independent adjudication committee. These occurred at levels of grade 1/2 (n = 13), grade 3 (n = 2), and grade 4 (n = 1). Four ILD or pneumonitis events had occurred since the primary analysis: 1 was grade 1 and the remaining 3 were grade 2.

The median time to first onset among the 16 ILD or pneumonitis events was 102.5 days (range, 36-638). One treatment-related death from pneumonia occurred in the trastuzumab deruxtecan arm, which had been reported in the primary analysis. No ILD or pneumonitis events or AE-related deaths occurred in the chemotherapy arm.

“This additional follow-up provides further evidence that trastuzumab deruxtecan is an effective treatment option for patients with HER2-positive advanced gastric cancer or GEJ adenocarcinoma who have progressed after 2 or more previous lines of therapy, including trastuzumab, fluoropyrimidine, and a platinum agent,” Yamaguchi said.

**REFERENCES**


**TABLE. Efficacy Outcomes From the DESTINY-Gastric01 Trial**

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab deruxtecan (n = 126)</th>
<th>Chemotherapy with irinotecan or paclitaxel (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, months</td>
<td>12.5</td>
<td>8.9</td>
</tr>
<tr>
<td>ORR by ICR (95% CI)</td>
<td>51.3% (41.9%-60.5%)</td>
<td>14.3% (6.4%-26.2%)</td>
</tr>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>42% (33%-51.4%)</td>
<td>12.5% (5.2%-24.1%)</td>
</tr>
<tr>
<td>Confirmed DCR (95% CI)</td>
<td>85.7% (78.1%-91.5%)</td>
<td>62.5% (48.5%-75.1%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>12.5 (5.6-NE)</td>
<td>3.9 (3.0-4.9)</td>
</tr>
<tr>
<td>Median TTR, months (95% CI)</td>
<td>1.5 (1.4-1.7)</td>
<td>1.6 (1.3-1.7)</td>
</tr>
</tbody>
</table>
For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted ADC monotherapy. So you can offer your RRMM patients a different option.

INDICATION

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes.

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS.

ADC = antibody–drug conjugate; BCMA = B-cell maturation antigen; RRMM = relapsed or refractory multiple myeloma.

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For appropriate patients faced with RRMM, BLENREP is the first and only BCMA-targeted ADC monotherapy. You can offer your RRMM patients a different option.

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Ocular Toxicity: Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%). Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4% of patients. Most decreased visual acuity of worse than 20/40, 88% recovered, and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction: Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity. Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist. Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery. BLENREP is only available through a restricted program under a REMS.

Thrombocytopenia: Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 4%, and Grade 4 in 1.4%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

Females and Males of Reproductive Potential: Based on findings in animal studies, BLENREP may impair fertility in females and males.

Geriatric Use: Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. The most common adverse reactions >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy testing is recommended for females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS

The pooled safety population described in "WARNINGS AND PRECAUTIONS" reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy (71%), decreased visual acuity (53%), nausea (24%), blurred vision (22%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%). The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased (22%), platelets decreased (21%), hemoglobin decreased (18%), neutrophils decreased (9%), creatinine increased (5%), and gamma-glutamyl transferase increased (5%).

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

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5.2 BLENREP REMS

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENREPREMS.com and 1-855-209-9188.

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 15%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)].

Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume infusion at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose, respectively [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

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

- Ocular toxicity [see Warnings and Precautions (5.1)].
- Thrombocytopenia [see Warnings and Precautions (5.3)].
- Infusion-related reactions [see Warnings and Precautions (5.4)].

6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2.

Of these patients, 194 received a liquid formulation (not the approved dosage form) of dosage and visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 or 4 keratopathy (n = 149), 38% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had keratopathy, 26% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Consider withholding BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3) of full Prescribing Information].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1) of full Prescribing Information].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)].
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dose interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dose interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (>20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (>5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 1 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

### Table 1. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Keratopathy*</td>
<td>71</td>
</tr>
<tr>
<td>Decreased visual acuity†</td>
<td>53</td>
</tr>
<tr>
<td>Blurred vision†</td>
<td>22</td>
</tr>
<tr>
<td>Dry eyes†</td>
<td>14</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
</tr>
<tr>
<td>Fatigue†</td>
<td>20</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions‡</td>
<td>21</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>11</td>
</tr>
<tr>
<td><strong>Metabolic and nutritional disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection‡</td>
<td>11</td>
</tr>
</tbody>
</table>

* Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
† Visual acuity changes were determined upon eye examination.
‡ Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
§ Dry eyes included dry eye, ocular discomfort, and eye pruritus.
§ Fatigue included fatigue and asthenia.
§ Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypertension, lethargy, tachycardia.
¶ Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:
- **Eye Disorders**: Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders**: Vomiting.
- **Infections**: Pneumonia.
- **Investigations**: Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

### Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-bllf1, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1)].

Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta, therefore, belantamab mafodotin-bllf1 has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. 

Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-bllf1. The cytotoxic component of BLENREP, MMAF: disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation
Risk Summary
There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential
BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing
Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception
Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility
Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

8.4 Pediatric Use
The safety and effectiveness of BLENREP in pediatric patients have not been established.

8.5 Geriatric Use
Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 75% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m2 as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR <15 mL/min/1.73 m2) or end-stage renal disease (ESRD) with dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin <upper limit of normal [ULN] and aspartate aminotransferase (AST) >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST). The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Medication Guide), Ocular Toxicity
• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Durvalumab Plus Chemotherapy Improves Survival in Advanced Biliary Tract Cancer

by JESSICA HERGERT

TREATMENT WITH THE PD-L1 INHIBITOR
durvalumab (Imfinzi®) in combination with gemicitabine and cisplatin resulted in significantly improved overall survival (OS) vs placebo plus chemotherapy in patients with advanced biliary tract cancer (BTC), according to results of the phase 3 TOPAZ-1 trial (NCT03875235) presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.1 2

The findings demonstrated a 20% reduction in the risk of death with durvalumab plus chemotherapy vs placebo plus chemotherapy in this patient population (HR, 0.80; 95% CI, 0.66-0.97; P = 0.021).

At a median follow-up of 13.7 months in the durvalumab-plus-chemotherapy arm (n = 341) and 12.6 months in the placebo-plus-chemotherapy arm (n = 344), the median OS was 12.8 months (95% CI, 11.1-14) vs 11.5 months (95% CI, 10.1-12.5), respectively. The 18-month OS rates were 35.1% (95% CI, 29.1%-41.2%) vs 25.6% (95% CI, 19.9%-31.7%), respectively. The 24-month OS rates were 24.9% (95% CI, 17.9%-32.5%) vs 10.4% (95% CI, 4.7%-18.8%), respectively.

“TOPAZ-1 is the first phase 3 trial to show that adding immunotherapy to standard chemotherapy can increase survival in BTC, and importantly, does so without inducing any new serious [adverse] effects,” lead study author Do-Youn Oh, MD, PhD, said in a news release.3 Oh is a professor in the Division of Medical Oncology of the Department of Internal Medicine at Seoul National University Hospital and Seoul National University College of Medicine in South Korea.

Gemicitabine plus cisplatin has been the standard chemotherapy option for patients with advanced BTC in the United States.1 However, immunogenic features of BTC indicate that checkpoint inhibitors may have clinical utility for this patient population, but limited clinical activity has been observed with single-agent therapy in the advanced setting.

“That standard has not changed in over a decade. TOPAZ-1 is the first phase 3 trial to demonstrate the benefit of immunotherapy for improved OS, in combination with chemotherapy, creating a new standard of care,” Cathy Eng, MD, FACP, FASCO, said in the news release.2 “Patients have a greater reason for hope given the positive results seen with the use of immunotherapy in [BTC].” Eng is the David H. Johnson Chair in Surgical and Medical Oncology at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee.

Because results of a phase 2 study demonstrated encouraging antitumor activity with durvalumab in combination with gemicitabine and cisplatin for patients with advanced BTC, the TOPAZ-1 trial was developed to further evaluate the immunotherapy-containing regimen vs chemotherapy alone.

The double-blind study randomized 685 patients with previously untreated, unresectable, locally advanced, recurrent, or metastatic BTC 1:1 to receive 1500 mg of durvalumab every 4 weeks or placebo until disease progression or unacceptable toxicity.1 Patients were stratified by disease status (initially unresectable vs recurrent) and primary tumor location (intrahepatic cholangiocarcinoma vs extrahepatic cholangiocarcinoma vs gallbladder cancer). Specifically among the study population, 55% of patients had intrahepatic cancers, 19% had extrahepatic cancers, and 25% had gallbladder cancer.

The median age was 64 years in both the durvalumab plus chemotherapy arm and the chemotherapy-alone arm, and approximately half of the patients in both arms had an ECOG performance status of 0 (50.7% vs 47.4%, respectively). The primary end point of the study was OS; secondary end points included progression-free survival (PFS), objective response rate (ORR), and safety.

Results showed that the median PFS was 7.2 months (95% CI, 6.7-7.4) with durvalumab plus chemotherapy vs 5.7 months (95% CI, 5.6-6.7) with placebo plus chemotherapy (HR, 0.75; 95% CI, 0.64-0.89; P = 0.001). The ORR was 26.7% with durvalumab plus chemotherapy compared with 18.7% for placebo plus chemotherapy.

Regarding safety, the most common adverse effects (AEs) included anemia (48.2%), neutropenia (31.7%), and nausea (40.2%). Potentially serious AEs were observed in 62.7% of patients receiving the durvalumab-containing regimen compared with 64.9% of patients receiving the placebo-containing regimen. This suggests that most AEs resulted from the chemotherapeutic agents.

Grade 3 or 4 AEs were observed in 75.7% of patients who received durvalumab plus chemotherapy (n = 338) compared with 77.8% of patients who received placebo plus chemotherapy (n = 342). Treatment-related AEs (TRAEs) leading to discontinuation of any drug were observed in 8.9% vs 11.4% of patients, respectively. TRAEs leading to death occurred in 0.6% vs 0.3% of patients, respectively.

“We are hopeful that durvalumab plus gemcitabine and cisplatin will become a new standard of care for advanced BTC,” Oh said in the news release. “Our first task at this time is boosting communication with patients and family members about the potential for this immunotherapy combination and what it may mean for their ongoing care.”

**TABLE. Efficacy Outcomes in the TOPAZ-1 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Durvalumab + gemcitabine/cisplatin (n = 341)</th>
<th>Placebo + gemcitabine/cisplatin (n = 344)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.8 (11.1-14)</td>
<td>11.5 (95% CI, 10.1-12.5)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>13.7</td>
<td>12.6</td>
</tr>
<tr>
<td>18-month OS rate, months (95% CI)</td>
<td>35.1% (29.1%-41.2%)</td>
<td>25.6% (19.9%-31.7%)</td>
</tr>
<tr>
<td>24-month OS rate, months (95% CI)</td>
<td>24.9% (17.9%-32.5%)</td>
<td>10.4% (4.7%-18.8%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.2 (6.7-7.4)</td>
<td>5.7 (5.6-6.7)</td>
</tr>
<tr>
<td>ORR</td>
<td>26.7%</td>
<td>18.7%</td>
</tr>
</tbody>
</table>

ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

**REFERENCES**

Adagrasib Monotherapy Elicits Encouraging Disease Control Rate in KRAS G12C–Mutant PDAC, GI Malignancies

by AUDREY STERNBERG

Adagrasib is a KRAS G12C–selective, covalent inhibitor with a long half-life that enables exposure above a target threshold throughout its activity. Continuous exposure to the agent above a target threshold leads to KRAS-dependent signaling inhibition and maximizes depth and duration of antitumor activity.

In total, 42 patients were enrolled in the KRYSTAL-1 trial at the data cutoff of September 10, 2021, with 30 having other GI tumors that harbored a KRAS G12C mutation (FIGURE). Of those, 12 patients had PDAC, 8 had biliary tract cancers, 5 had appendiceal cancers, 2 had gastroesophageal junction cancers, 2 had small-bowel cancers, and 1 had esophageal cancer. The median age was 65.5 years (range, 40-89). Most patients had an ECOG performance status of 1 (80%) and a median of 2 prior lines of therapy (range, 1-5).

Previously reported data from the multicohort phase 1/2 trial established clinical activity with adagrasib in various solid tumors, including GI malignancies, lung cancers, and gynecologic cancers.

Patients were treated with the recommended phase 2 dose of 600-mg adagrasib twice daily. The primary end point of the phase 2 portion included objective response rate, with duration of response (DOR), progression-free survival (PFS), overall survival, and safety as secondary end points.

In the PDAC group, the median time to response (TTR) was 2.8 months and the median DOR was 6.97 months. The median PFS was 7.85 months. The median TTR of 1.3 months and a median DOR of 7.85 months. The median PFS was 7.85 months (95% CI, 6.9-11.3), and 65% of patients (n = 11) were still receiving treatment at the time of data cutoff. “When you look at biliary tract cancer, 50% of the patients had [a] response,” Bekaii-Saab said. “These are small numbers, but these are solid responses.”

### TABLE. Commonly Reported TRAEs in the KRYSTAL-1 Trial

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any grade (n = 42)</th>
<th>Grade 3 (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea 48%</td>
<td>Fatigue 7%</td>
</tr>
<tr>
<td></td>
<td>Vomiting 43%</td>
<td>QTC prolongation 5%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea 43%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue 29%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate aminotransferase increase 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood creatinine increase 19%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia 17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral edema 17%</td>
<td></td>
</tr>
</tbody>
</table>

TRAEs, treatment-related adverse events.

### FIGURE. Patient Characteristics in the KRYSTAL-1 Trial

- PDAC
- Biliary tract
- Appendiceal
- GEJ
- Small bowel
- Esophageal

GI, gastrointestinal; GEJ, gastro-esophageal junction; PDAC, pancreatic ductal adenocarcinoma.

- Median age at baseline, years (range): 65.5 (40-89)
- ECOG performance status at baseline: 80% (0), 20% (1)
- Median prior lines of therapy at baseline (range): 2 (1-5)
As for safety, no grade 4 or greater toxicities were noted, and few non-GI adverse events occurred in the PDAC cohort.

In the overall cohort, treatment-related adverse events (TRAEs) occurred in 91% of patients (n = 38/42). The most-reported any-grade TRAEs were nausea (48%), vomiting (43%), diarrhea (43%), fatigue (29%), aspartate aminotransferase increase (19%), blood creatinine increase (19%), anemia (17%), and peripheral edema (17%). The most commonly reported grade 3 events were fatigue (7%) and corrected QT interval prolongation (5%) (TABLE).1

Regarding next steps for adagrasib, a newly initiated expanded access trial (NCT05162443) is open for enrollment for patients with KRAS G12C-mutant solid tumors for whom no other treatments are available.1

### REFERENCES


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**Durvalumab Plus Tremelimumab Elicits Superior OS Over Monotherapy Options in Unresectable HCC**

by CAROLINE SEYMOUR

**ACCORDING TO FINDINGS FROM** the final analysis of the HIMALAYA trial (NCT03298451), the combination of durvalumab (Imfinzi) and tremelimumab demonstrated a significant improvement in overall survival (OS) vs standard-of-care sorafenib (Nexavar) as frontline therapy for patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy and are not eligible for locoregional therapy. Results were presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.1

At data cutoff, the combination of durvalumab and tremelimumab showed a 22% reduction in the risk of death compared with sorafenib, meeting the primary end point of the phase 3 study (HR, 0.78; 96% CI, 0.65-0.92; P = .0035). Specifically, the median OS was 16.4 months (95% CI, 14.2-19.6) with durvalumab and tremelimumab, 16.6 months (95% CI, 14.1-19.1) with durvalumab, and 13.8 months (95% CI, 12.3-16.1) with sorafenib. Of note, treatment with durvalumab alone demonstrated noninferior OS vs sorafenib (HR, 0.86; 95.07% CI, 0.73-1.03).

**TABLE 1. Efficacy Outcomes in the HIMALAYA Trial**1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Durvalumab plus durvalumab (n = 393)</th>
<th>Durvalumab (n = 389)</th>
<th>Sorafenib (n = 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>16.4 (14.2-19.6)</td>
<td>16.6 (14.1-19.1)</td>
<td>13.8 (12.3-16.1)</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>16.1</td>
<td>16.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Deaths at data cutoff</td>
<td>66.7%</td>
<td>72%</td>
<td>75.3%</td>
</tr>
<tr>
<td>24-month OS</td>
<td>40.5%</td>
<td>39.6%</td>
<td>32.6%</td>
</tr>
<tr>
<td>36-month OS</td>
<td>30.7%</td>
<td>24.7%</td>
<td>20.2%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.8 (3.7-5.3)</td>
<td>3.7 (3.2-3.8)</td>
<td>4.1 (3.8-5.5)</td>
</tr>
<tr>
<td>ORR</td>
<td>20.1%</td>
<td>17%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>22.3</td>
<td>16.8</td>
<td>18.4</td>
</tr>
</tbody>
</table>

Additional results showed that the 24-month OS rate was 40.5% with durvalumab and tremelimumab (n = 393), 39.6% with durvalumab (n = 389), and 32.6% with sorafenib (n = 389). The 36-month OS rates were 30.7%, 24.7%, and 20.2%, respectively (TABLE).1

“Pending FDA approval, this novel dual immunotherapy regimen could be readily available to all patients and would not require additional safety assessments prior to treatment,” said lead study author Ghassan K. Abou-Alfa, MD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, in a news release.1

In January 2020, the FDA granted an orphan drug designation to durvalumab plus tremelimumab for the treatment of patients with HCC.3 At the start of the HIMALAYA trial, sorafenib was the only approved frontline standard of care for patients with advanced HCC. Now lenvatinib (Lenvima) and atezolizumab (Tecentriq) plus bevacizumab (Avastin) are also approved for use as frontline therapy.3

Investigators established the rationale for combining the anti–CTLA-4 agent tremelimumab with the anti–PD-L1 agent durvalumab based on findings from a phase 2 study (NCT02519348). That regimen—which included a single high-dosing dose (300 mg) of tremelumab plus 1500 mg of durvalumab every 4 weeks—demonstrated encouraging activity in patients with unresectable HCC, with a confirmed objective response rate (ORR) of 24% (95% CI, 14.9%-35.3%) and a median OS of 18.7 months (95% CI, 10.8-27.3).4

Investigators of the randomized, open-label, multicenter HIMALAYA study then evaluated the efficacy and safety of the tremelimumab and durvalumab regimen, durvalumab alone, and sorafenib alone in patients with unresectable HCC who had not received prior systemic therapy and who were not eligible for locoregional therapy.1 Patients with known risk factors for the disease were included in the trial, including those with viral hepatitis B, hepatitis C, and other nonviral origins. Secondary end points of HIMALAYA included progression-free survival (PFS), ORR per RECIST 1.1 criteria, duration of response (DOR), time to progression, and disease control rate.

The median age in the combination arm was 65 years (range, 22-86), 64 years (range, 20-86) in the durvalumab arm, and 64 years (range, 18-88) in the sorafenib arm. A majority of patients had Child-Pugh class A disease (99.7%, 99.7%, and 99.2%, respectively). The median PFS was 3.78 months (95% CI, 3.68-5.32) with durvalumab and tremelimumab, 3.65 months (95% CI, 3.19-3.75) with durvalumab, and 4.07 months (95% CI, 3.75-5.49) with sorafenib. The HR for the combination vs sorafenib was 0.90 (95% CI, 0.77-1.05) and the HR for durvalumab alone vs sorafenib was 1.02 (95% CI, 0.88-1.19).

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**Ghassan K. Abou-Alfa, MD**
The ORR was higher with durvalumab and tremelimumab (20.1%) and with durvalumab alone (17.0%) vs sorafenib (5.1%). Specifically, in the combination arm, 3.1% of responders had a complete response (CR), 17.0% had a partial response (PR), and 39.9% of patients had both stable disease (SD) and progressive disease (PD). In the durvalumab arm, 1.5% of patients had a CR, 15.4% had a PR, 37.8% had SD, and 45.2% had PD. In the sorafenib arm no patients had a CR. 5.1% had a PR, 55.5% had SD, and 39.3% had PD. This translated to a disease control rate of 60.1% in the durvalumab and tremelimumab arm, 54.8% in the durvalumab arm, and 60.7% in the sorafenib arm.

The median DORs were 22.3 months, 16.8 months, and 18.4 months in the durvalumab and tremelimumab, durvalumab, and sorafenib arms, respectively. Further, the median time to progression was 5.42 months (95% CI, 3.81-5.62) with the combination, 3.75 months (95% CI, 3.68-5.42) with durvalumab alone, and 5.55 months (95% CI, 5.13-5.75) with sorafenib.

Regarding safety, grade 3/4 treatment-related adverse effects (TRAEs) occurred in 25.8% of patients receiving durvalumab and tremelimumab, 12.9% of patients receiving durvalumab alone, and in 36.9% receiving sorafenib. Grade 3/4 hepatic TRAEs occurred in 5.9%, 5.2%, and 4.5% of patients, respectively.

Additionally, serious TRAEs occurred in 3.1% of patients in the durvalumab and tremelimumab arm, 8.2% of patients in the durvalumab arm, and 9.4% of patients in the sorafenib arm. Grade 5 TRAEs occurred in 2.3%, 0%, and 0.8% of patients, respectively. TRAEs leading to discontinuation occurred in 8.2% of patients receiving durvalumab and tremelimumab, 4.1% of patients receiving durvalumab, and in 11% receiving sorafenib (TABLE 2).1

“TO date, the HIMALAYA study is one of the largest phase 3 studies conducted with long-term follow-up demonstrating the role of immunotherapy in surgically unresectable HCC,” said Cathy Eng, MD, FACP, FASCO, the David H. Johnson Chair in Surgical and Medical Oncology at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, in a news release. “HIMALAYA chose a novel approach of priming with a single dose of combination immunotherapy followed by the single agent durvalumab. While the primary end point was met, based on the current data, the secondary end point of PFS was not superior in either investigational arm relative to the control arm, requiring further discussion.”2

The findings. Metges is an associate professor of cancerology at Brest University Hospital Center-Morvan Hospital in France.

Among patients in the intention-to-treat population 186 who received pembrolizumab and 197 who received placebo had a PD-L1 combined positive score (CPS) of 10 or higher. The median OS was 13.6 months (95% CI, 11.1-15.2) for those in the experimental arm compared with 9.4 months (95% CI, 8.0-10.7) for those in the control arm (HR, 0.64; 95% CI, 0.51-0.80). The 12-month OS rate was 54% in the pembrolizumab arm vs 30% in the placebo arm. The 24-month OS rates were 37% and 16%, respectively.

A prespecified subgroup analysis of patients with ESCC histology was an additional primary end point of the study. Among all patients with ESCC the median OS obtained was
12.6 months for those who received pembrolizumab (n = 274) and 9.8 months for those who received placebo (n = 274; HR, 0.73; 95% CI, 0.63-0.86). The 12-month OS rates were 51% vs 38%, respectively, and the 24-month OS rates were 27% vs 17%.

In the subgroup of patients with ESCC who had a PD-L1 CPS of 10 or higher, the median OS was 13.9 months (95% CI, 11.1-16.0) for those who received pembrolizumab (n = 143) vs 8.8 months (95% CI, 7.6-10.5) for those who received placebo (n = 143; HR, 0.59; 95% CI, 0.45-0.76). The 12- and 24-month OS rates were 55% and 29% for patients who received pembrolizumab, and 35% and 15% for those who received placebo.

In the ESCC subgroup, the median PFS was 6.3 months (95% CI, 6.2-7.1) with pembrolizumab vs 5.8 months (95% CI, 5.0-6.1) with chemotherapy alone (HR, 0.65; 95% CI, 0.54-0.78). The 12-month PFS rates were 24% vs 12%, respectively, and the 24-month PFS rates were 12% vs 4%. In the subgroup with a PD-L1 CPS of 10 or higher, the median PFS was 7.5 months (95% CI, 6.2-8.2) vs 5.5 months (95% CI, 4.3-6.0), respectively (HR, 0.51; 95% CI, 0.41-0.65). The 12- and 24-month PFS rates were 30% and 15%, respectively, among those who received pembrolizumab compared with 9% and 4% among those who received placebo, respectively (TABLES 1, 2).1

In March 2021, the FDA approved pembrolizumab for use in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal or gastroesophageal carcinoma who are ineligible for surgical resection or definitive chemoradiation. The decision was based on earlier findings from the phase 3, randomized, double-blind KEYNOTE-590 trial.2

Overall, 749 treatment-naïve patients with advanced, unresectable, or metastatic adenocarcinoma, ESCC, or Siewert type 1 EGJ, were randomly assigned 1:1 to receive either 200 mg of pembrolizumab once every 3 weeks for up to 24 months plus chemotherapy or placebo once every 3 weeks for up to 24 months plus chemotherapy. Chemotherapy consisted of 5-fluorouracil at 800 mg/m² intravenously (IV) for days 1 to 5 every 3 weeks for 35 or fewer cycles plus cisplatin at 80 mg/m² IV every 3 weeks for 6 or fewer cycles.

In the experimental group, 1 patient was continuing treatment at the time of data cutoff; 33 patients completed therapy and 336 discontinued therapy. In the control group, 5 patients completed therapy and 363 have discontinued treatment. The primary end points were OS in patients with ESCC who had a PD-L1 CPS of 10 or higher, and OS and PFS per RECIST 1.1 by investigator assessment. Secondary end points included overall response rate (ORR), duration of response (DOR), safety, and quality of life (QOL). The ORRs for the combination and control cohorts were 45% and 29.3%, respectively. Specifically, the complete response rates were 6.7% vs 2.4% and the partial response rates were 38.3% vs 26.9%. In the investigative and control arms, stable disease was reported among 33.8% vs 46.3% of patients, respectively, and progressive disease was noted among 11.5% vs 15.7% of patients. The disease control rates were 78.8% vs 75.5%, respectively. Further, 9.6% of patients receiving pembrolizumab plus chemotherapy and 8.7% of patients receiving chemotherapy alone did not exhibit evaluable antitumor response.

The median DOR was 8.3 months (range, 1.2-41.7) in the investigative group and 6 months (range, 1.5-34.9) in the control group. The median PFS was 20.4 months (95% CI, 16.9-23.8) in the investigative group and 12.6 months (95% CI, 10.2-14.2) in the control group. The OS at 12 months was 51% vs 39% for patients who received pembrolizumab and 39% vs 24% for those who received placebo, respectively.

In the subgroup of patients with ESCC who had a PD-L1 CPS of 10 or higher, the median OS was 13.9 months (95% CI, 11.1-16.0) for those who received pembrolizumab (n = 143) vs 8.8 months (95% CI, 7.6-10.5) for those who received placebo (n = 143; HR, 0.59; 95% CI, 0.45-0.76). The 12- and 24-month OS rates were 55% and 29% for patients who received pembrolizumab, and 35% and 15% for those who received placebo.

In the ESCC subgroup, the median PFS was 6.3 months (95% CI, 6.2-7.1) with pembrolizumab vs 5.8 months (95% CI, 5.0-6.1) with chemotherapy alone (HR, 0.65; 95% CI, 0.54-0.78). The 12-month PFS rates were 24% vs 12%, respectively, and the 24-month PFS rates were 12% vs 4%. In the subgroup with a PD-L1 CPS of 10 or higher, the median PFS was 7.5 months (95% CI, 6.2-8.2) vs 5.5 months (95% CI, 4.3-6.0), respectively (HR, 0.51; 95% CI, 0.41-0.65). The 12- and 24-month PFS rates were 30% and 15%, respectively, among those who received pembrolizumab compared with 9% and 4% among those who received placebo, respectively (TABLES 1, 2).1

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Overall, 749 treatment-naïve patients with advanced, unresectable, or metastatic adenocarcinoma, ESCC, or Siewert type 1 EGJ, were randomly assigned 1:1 to receive either 200 mg of pembrolizumab once every 3 weeks for up to 24 months plus chemotherapy or placebo once every 3 weeks for up to 24 months plus chemotherapy. Chemotherapy consisted of 5-fluorouracil at 800 mg/m² intravenously (IV) for days 1 to 5 every 3 weeks for 35 or fewer cycles plus cisplatin at 80 mg/m² IV every 3 weeks for 6 or fewer cycles.

In the experimental group, 1 patient was continuing treatment at the time of data cutoff; 33 patients completed therapy and 336 discontinued therapy. In the control group, 5 patients completed therapy and 363 have discontinued treatment. The primary end points were OS in patients with ESCC who had a PD-L1 CPS of 10 or higher, and OS and PFS per RECIST 1.1 by investigator assessment. Secondary end points included overall response rate (ORR), duration of response (DOR), safety, and quality of life (QOL). The ORRs for the combination and control cohorts were 45% and 29.3%, respectively. Specifically, the complete response rates were 6.7% vs 2.4% and the partial response rates were 38.3% vs 26.9%. In the investigative and control arms, stable disease was reported among 33.8% vs 46.3% of patients, respectively, and progressive disease was noted among 11.5% vs 15.7% of patients. The disease control rates were 78.8% vs 75.5%, respectively. Further, 9.6% of patients receiving pembrolizumab plus chemotherapy and 8.7% of patients receiving chemotherapy alone did not exhibit evaluable antitumor response.

The median DOR was 8.3 months (range, 1.2-41.7) in the investigative group and 6 months (range, 1.5-34.9) in the control group. The median PFS was 20.4 months (95% CI, 16.9-23.8) in the investigative group and 12.6 months (95% CI, 10.2-14.2) in the control group. The OS at 12 months was 51% vs 39% for patients who received pembrolizumab and 39% vs 24% for those who received placebo, respectively.
Nivolumab Plus Encorafenib and Cetuximab Elicits Notable Response Rate in MSS, BRAF V600E–Mutant mCRC

by MATTHEW FOWLER

THE ADDITION OF NIVOLUMAB (Opdivo) to encorafenib (Braftovi) and cetuximab (Erbitux) resulted in a significant response rate and an acceptable safety profile in patients with refractory microsatellite stable (MSS), BRAF V600E–mutant metastatic colorectal cancer (mCRC), according to study findings presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.

Data from the phase 1/2 trial (NCT04017650) highlighted an overall response rate (ORR) of 50% (95% CI, 28%-72%) among those treated with the triplet (n = 22), with all patients achieving partial responses. Additionally, no dose-limiting toxicities occurred. Grade 3/4 treatment-related adverse events (AEs) occurred in 4 patients (18%).

“Encorafenib, cetuximab, and nivolumab appears to be a safe and well-tolerated combination for patients with microsatellite stable BRAF-mutated mCRC,” Van K. Morris, MD, a lead study investigator said in a presentation of the data. “The efficacy of this combination appears promising when considering the precedent of encorafenib and cetuximab alone from the previously reported BEACON study [NCT02928224].” Morris is an assistant professor in the Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston.

To be eligible to enroll in the study, patients with MSS BRAF V600E–mutant mCRC were required to have received 1 or 2 prior lines of systemic therapy and have an ECOG performance status of 0 or 1. Patients who received prior treatment with a BRAF, MEK, ERK, anti-EGFR, or immune-checkpoint therapy were excluded.

The investigators treated 26 patients as per the trial protocol, all of whom were evaluable for safety and 22 of whom were evaluable for response. The median age of the total population was 58 years (range, 32-85). Most patients had right-sided primary tumors (62%) and had received 1 prior line of therapy (62%). Investigators reported an even split between those who had an ECOG performance status of 0 and 1.

The study regimen included a 300-mg dose of oral encorafenib daily, 500 mg/m² of intravenous (IV) cetuximab every 14 days, and 480 mg of IV nivolumab every 28 days. The primary end points of the study were best overall response rate per RECIST 1.1 criteria and safety and tolerability. Key secondary end points included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR).

Regarding safety, common AEs of any grade included headache (65%), nausea (35%), maculopapular rash (31%), arthralgia (27%), acneiform rash (27%), chills (23%), and precancerous skin lesions (23%). Grade 3 AEs, seen in 1 patient each, included colitis, maculopapular rash, asymptomatic elevated amylase and lipase, and leukocytosis. The only grade 4 AE, observed in 1 patient, was myositis and myocarditis.

As for secondary end points, at a median follow-up time of 16.3 months (95% CI, 6.9-not applicable [NA]), the median PFS was 7.4 months (95% CI, 5.6-NA) and the median OS was 15.1 months (95% CI, 7.7-NA). Additionally, the DCR was 96% (95% CI, 77%-100%) and the median duration of response was 7.7 months (95% CI, 3.8-NA).

“For patients who are experiencing responses, there is continued reduction in tumor size across the period of treatment,” Morris said. “[Of] the 11 patients who continue to remain on study, 2... remain on treatment with encorafenib, cetuximab, and nivolumab at 100 weeks.”

REFERENCE

REFERENCES

For more in-depth coverage from the 2022 American Society of Clinical Oncology Gastrointestinal (GI) Cancers Symposium and exclusive interviews with experts in GI cancers, scan the QR code or go to bit.ly/3ogfamV
WHAT’S NOW vs WHAT’S NEXT

PD-1 inhibition has delivered benefits for some patients, but not for others.¹²

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Novartis, the first to deliver FDA-approved TKI, CAR-T, and radioligand therapies to patients with cancer, is now continuing its legacy of innovation by exploring PD-1 inhibition and novel combination regimens. Our clinical development program leverages these diverse modalities, but also goes beyond these therapies.³⁷

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First-in-Class AR Agonist Opens Doors for ER-Positive Metastatic Breast Cancer

**Clinical Trial In Focus**

**BREAST CANCER**

**ANDROGEN RECEPTOR (AR) POSITIVITY** serves as an independent predictor of beneficial outcomes in breast cancer. Although AR is expressed in up to 90% of patients with estrogen receptor (ER)-positive breast cancer, successful efforts to optimize it in this population have been limited. However, early preclinical data have uncovered a new approach for leveraging AR, representing a potential opportunity to fill the unmet need for patients with ER-positive disease who have exhausted available treatments.1,2

Data from patient-derived models showed that AR agonism, rather than antagonism, durably inhibited tumor growth, contextualizing why progress incorporating AR-targeted therapies has been constrained.2 Investigators concluded that this finding illuminates the potential role for AR in ER-positive breast cancers with the development of selective AR agonists.

“The way that AR works in an ER-positive cell has been a mystery and is not completely clear,” said Lee S. Schwartzberg, MD, FACP, in an interview with OncologyLive®. “We now believe that in [patients who have] hormone receptor-positive disease, the AR functions more as a tumor suppressor gene. It’s not [as though] if you suppress ER, as we do with most of our endocrine therapies, that the androgen turns on like it does in prostate cancer. It seems to have a different role in this group of patients. In the past, we’ve tested blockers of AR based on what was probably an erroneous principle—that it could be a resistance mechanism by signaling through AR as opposed to receptor hormone. We used drugs like enzalutamide [Xtandi] and other drugs that inhibited androgens either directly or [through] the production of androgens like fulvestrant [Faslodex], which were also used in the past. It turned out [that those drugs] didn’t have a great benefit in that setting.”

In an effort to develop a new class of agents to test this preclinical hypothesis, investigators developed enobosarm, a first-in-class, novel oral selective AR-targeting agonist. “In AR-positive, hormone receptor-positive preclinical models, enobosarm has a profound effect at inhibiting the growth of cancers, and that’s true in cell lines that are estrogen sensitive and estrogen resistant,” said Schwartzberg, chief medical officer and a board member at OneOncology. He added that data from mouse models also demonstrated that enobosarm combines well with CDK4/6 inhibitors, which led to the rationale to carry the agent over to in-human studies for patients with metastatic breast cancer.2

**ESTABLISHING A PATH FORWARD FOR AR AGONISTS**

Investigators initiated trials for patients with AR-positive metastatic breast cancer, including those with triple-negative breast cancer. “The AR [tumor suppressor pathway] is intriguing,” said Sara M. Tolaney, MD, MPH said. “In data for enobosarm we saw that there was robust clinical benefit from this agent in pretreated hormone receptor-positive breast cancer. What we saw was that the activity was even greater when you looked at patients who had high AR expression. The investigators used an AR expression cutoff of greater than or equal to 40% and that’s where they started seeing their objective responses.” Tolaney is chief of the Division of Breast Oncology and associate director at Susan F. Smith Center for Women’s Cancers, a senior physician at Dana-Farber Cancer Institute, and an associate professor of medicine at Harvard Medical School in Boston, Massachusetts.

Data from 2 trials in particular concerning AR-positive, ER-positive metastatic breast cancer provided the rationale for commencing a phase 3 trial. First, in a phase 2, single-arm, proof-of-concept study (NCT01616758), investigators examined enobosarm at a dose of 9 mg daily for the treatment of patients with AR-positive, ER-advanced breast cancer. The primary end point, clinical benefit rate (CBR) at 24 weeks, was met at 35.3% (90% CI, 16.6%-58%) among 22 treated patients. At day 84, the progression-free survival probability was 57.7% and was 50.5% at day 168; the 6-month Kaplan-Meier estimate for progression-free survival (PFS) was 43.8%.3 In terms of safety, the agent was well tolerated with no significant virilizing effects and no reported liver toxicity.

**FIGURE. Enobosarm for the Treatment of AR-positive, ER-positive, HER2-negative MBC**

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
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<tbody>
<tr>
<td>≥ 18 years</td>
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<tr>
<td>ECOG performance status of ≤ 2</td>
</tr>
<tr>
<td>Measurable disease per RECIST 1.1</td>
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<tr>
<td>AR nuclei staining ≥ 40% as assessed by central laboratory</td>
</tr>
<tr>
<td>Received at least 2 prior lines of treatment in MBC setting which must have included both an AI (monotherapy or combination) and fulvestrant (monotherapy or combination); at least 1 must have been given in combination with a CDK 4/6 inhibitor</td>
</tr>
<tr>
<td>Previously responded (without disease progression for at least 6 months) to 1 of the following treatments: fulvestrant monotherapy or fulvestrant plus CDK 4/6 inhibitor or nonsteroidal AI monotherapy or nonsteroidal AI plus CDK 4/6 inhibitor for metastatic breast cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>rPFS</td>
</tr>
<tr>
<td>Select secondary</td>
</tr>
<tr>
<td>ORR</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; AR, androgen receptor; ER, estrogen receptor; MBC, metastatic breast cancer; ORR, objective response rate; rPFS, radiographic progression-free survival.
In a second phase 2 study (NCT02463032), investigators evaluated patients with heavily pretreated AR-positive, ER-positive, HER2-negative metastatic breast cancer who had progressed after treatment with multiple lines of endocrine therapy. The open-label, multinational trial enrolled 136 postmenopausal women to be treated with enobosarm 9 mg (n = 72) or enobosarm 18 mg (n = 64). The primary efficacy end point of the study was to determine CBR by RECIST 1.1 criteria at 6 months.¹

The median age in the 9-mg cohort was 60.5 years (range, 35-83) and 62.5 years (range, 42-81) in the 18-mg cohort. Prior chemotherapy had been administered in 90% and 92.3% of patients in the 9-mg group (n = 50) and the 18-mg group (n = 52), respectively. The median number of prior lines of endocrine therapy among all patients was 3. Among those in the 9-mg cohort, the CBR at 24 weeks was 32% (95% CI, 19.5%-46.7%). The 24-week CBR in the 18-mg cohort (n = 52) was 29% (95% CI, 17.1%-43.1%).¹

Investigators observed a correlation between radiographic PFS (rPFS) and AR nuclei staining. In an exploratory analysis, they determined that 40% AR staining was the optimal cutoff. The median rPFS for patients with greater than 40% AR staining (n = 24) was 5.5 months compared with 2.75 months among patients with less than 40% AR staining (n = 22). The ORR was 50% vs 0%, respectively, and the CBRs were 79% vs 18%, respectively (P < .0001).¹

In terms of safety, most adverse effects (AEs) reported in the study were grade 1/2. Serious AEs occurred at a rate of 10.7% vs 16.4% in the 9-mg arm and 18-mg arm, respectively.

“The 9-mg dose turned out to be the better dose; it was a little less toxic and had at least as good activity with numerically better efficacy than the 18-mg dose,” said Schwartzberg. “Enobosarm is clearly an active agent that has relatively little toxicity. Most of the AEs that were seen in that phase 2 trial were mostly grade 1 and 2; there were a few increased liver function tests from enobosarm, and hypercalcemia was seen in some patients. That was the dose-limiting toxicity early on, but that was only seen in a couple of patients and was easily managed.”

Based on these data, the dose for phase 3 trials was determined to be 9 mg and the threshold for AR positivity was set at a minimum of 40% AR nuclei staining. Schwartzberg noted that testing for AR is commercially available. “It’s used in other diseases such as prostate cancer [and] can be done in any pathology lab,” he said.

### VALIDATING ENOBOSARM FOR CLINICAL USE

In the phase 3 ARTEST trial (NCT04869943), investigators are examining the efficacy of enobosarm vs physician’s choice of endocrine therapy in patients with AR-positive, ER-positive, and HER2-negative metastatic breast cancer who have experienced tumor progression after treatment with estrogen-blocking agents and CDK 4/6 inhibitors (FIGURE).³ Physician’s choice therapy includes treatments such as exemestane, exemestane and everolimus (Afinitor), or selective ER modulators including tamoxifen.

The primary end point of the trial is median rPFS defined by RECIST 1.1 criteria. The secondary end point is objective response rate.

Eligibility criteria for the study include an ECOG performance status of 2 or lower and at least 2 prior lines of therapy including treatment with an aromatase inhibitor and fulvestrant, both as a monotherapy or in combination with another treatment. At least one of the therapies must have been administered in combination with a CDK4/6 inhibitor.² Of note, participants may have received 1 course of chemotherapy in the adjuvant or neoadjuvant setting which would not count as a line of therapy.

“If enobosarm shows activity that is better than the endocrine therapy of physician’s choice, this will be an important treatment modality in our armamentarium.”

—LEE S. SCHWARTZBERG, MD, FACP

are going to be curative. We also know now that patients do very well with endocrine therapy for a prolonged period. If we can get another agent that works in a completely different mechanism for these patients who are ER positive, we can potentially prolong their time to live and prolong their time until they need chemotherapy. Everyone agrees that endocrine therapy is kinder and gentler and often more effective than chemotherapy in this large subgroup of patients who are ER positive, HER2 negative with advanced breast cancer.”²

The first patient was enrolled in the ARTEST trial in October 2021.³ On January 10, 2022, Veru Inc, the developer of enobosarm, announced that the FDA had granted a fast track designation to the phase 3 registration program for the agent.⁴

“We always need to look back into history and try to elevate some of the seminal clinical observations that were made in the past and repurpose them now in a modern era. Enobosarm is an evolution of what we knew 40 years ago in breast cancer—that the androgen axis is important and can be manipulated to improve the outcomes of some patients with breast cancer. I’m very excited about [the research that’s to come],” said Schwartzberg.

**REFERENCES**


INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:
- adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

IMPORTANT SAFETY INFORMATION
Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 5.3% of patients, including Grade 3 or 4 events in 3% and increased alanine aminotransferase (ALT) occurred in 4.6% of patients, including Grade 3 or 4 events in 3%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 1.7% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertensive medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Please see Important Safety Information and Brief Summary of Prescribing Information for Retevmo on subsequent pages.
Response in patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC), advanced or metastatic RET fusion-positive thyroid cancer (non-MTC),* and advanced or metastatic RET-mutant MTC1

<table>
<thead>
<tr>
<th>Treatment naive (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
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<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 70.94) 0% CR + 85% PR</td>
<td>(95% CI: 54.73) 1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12.7 NE) median follow-up: 7.4 months&lt;sup&gt;1,1&lt;/sup&gt;</td>
<td>(95% CI: 12. NE) median follow-up: 12.1 months&lt;sup&gt;1,1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Metastatic RET Fusion-Positive NSCLC**

**Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases**<sup>1</sup>

CNS DoR was ≥6 months in all responders with measurable brain metastases<sup>1</sup>

No patients received radiation therapy to the brain within 2 months prior to study entry<sup>1</sup>

**Advanced or Metastatic RET Fusion-Positive Thyroid Cancer (Non-MTC)**

Systemic therapy naive<sup>1</sup> (n=8)  

**100% ORR**<sup>1</sup>  

(95% CI: 61.100) 12.5% CR + 88% PR

**Median DoR not yet reached**  

(95% CI: NE, NE) median follow-up: 8.8 months<sup>1,1</sup>

Previously treated<sup>1</sup> (n=19)

**79% ORR**<sup>1</sup>  

(95% CI: 54.94) 5.3% CR + 74% PR

**Median DoR was 18.4 months**  

(95% CI: 76.7 NE) median follow-up: 17.3 months<sup>1,1</sup>

**Advanced or Metastatic RET-Mutant MTC**

Previously treated with cabozantinib and/or vandetanib (n=55)

**73% ORR**<sup>1</sup>  

(95% CI: 62.82) 11% CR + 61% PR

**Median DoR was 22.0 months**  

(95% CI: NE, NE) median follow-up: 7.8 months<sup>1,1</sup>

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**Adverse Reactions and Laboratory Abnormalities**

- The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation.

- Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3). Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received Retevmo. Adverse reactions resulting in permanent discontinuation in patients who received Retevmo included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

- Dose interruptions due to an adverse reaction occurred in 42% of patients who received Retevmo. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

- Dose reductions due to an adverse reaction occurred in 31% of patients who received Retevmo. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation, and fatigue.
IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib 40 mg. 80 mg capsules) (CONT’D)

Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diabetes. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Other hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 0.4% patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminists. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rabbits during organogenesis at a maternal dose (mg/kg) equal to or less than the human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3–4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were hypertension (18%), prolonged QT interval (4%), diarrhea (3%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients: fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001 were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (33%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades, Grade 3–4): ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001 were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (45%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.6%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (56%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), increased uric acid (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of acid-reducing agents decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of strong and moderate CYP3A inhibitors increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of strong and moderate CYP3A inducers decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with CYP2CB and CYP3A substrates increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid concomitant use of strong and moderate CYP3A substrates with Retevmo. If coadministration cannot be avoided, follow recommendations for CYP2CB and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in pediatric patients less than 12 years of age. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older.

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance (CLcr) ≥ 30 mL/Min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

Reduce the dose when administering Retevmo to patients with severe hepatic impairment (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

SE HCP ISI AL_25AU2G2020

Please see Brief Summary of Prescribing Information for Retevmo on subsequent pages.

Retevmo™ (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020

BRIEF SUMMARY: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE
Retevmo (selpercatinib) is a kinase inhibitor indicated for the treatment of:
- Adult patients with metastatic RET-fusion positive non-small cell lung cancer (NSCLC) who have progressed on platinum-based therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion positive medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion positive thyroid cancer who require systemic therapy are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 in 4% and increased ALT occurred in 45% of patients, including Grade 3 in 4% and increased AST in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity.

Hypertension
Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity.

QT Interval Prolongation
RETEVMO can cause concentration-dependent QT interval prolongation. An increase in QTf interval (≥500 ms) was measured in 6% of patients and an increase in the QTf interval of at least 60 ms over baseline was measured in 15% of patients. RETEVMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at risk of developing QTc prolongation, including patients with known QT syndrome, clinically significant bradycardia, and severe or uncontrolled heart failure. Avoid QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based on risk factors including diuretics. Correct hypokalemia, hypomagnesemia and hypocalemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A4 inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with RETEVMO including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoperitoneum.

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage.

Hyperosmolality
Hyperosmolality occurred in 4.2% of patients receiving RETEVMO, including Grade 3 hyperosmolality in 1.5%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hyperosmolality included thirst and headache or myalgia with concurrent decreased platelets or transaminases.

If hyperosmolality occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hyperosmolality. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hyperosmolality.

Retevmo™ (selpercatinib) capsules, for oral use

Table 1: Adverse Reactions (≥1%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
<th>Grades 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>38</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain‡</td>
<td>23</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 summarizes the adverse reactions in LIBRETTO-001.

Table 1: Adverse Reactions (≥1%) in Patients Who Received RETEVMO in LIBRETTO-001

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<td>35</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of RETEVMO after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity
Based on data from animal reproduction studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg orally twice daily resulted in embryo-fetal malformations. Advise pregnant women of the potential risk to a fetus. Advise female reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for at least 1 week after the final dose.

ADVERSE REACTIONS

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

RET Gene Fusion or Gene Mutation Positive Solid Tumors
The pooled safety population described in the WARNINGS and PRECAUTIONS below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETEVMO, 62% were exposed for 4 months or longer and 34% were exposed for greater than one year. Among these patients, 50% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 52% were male; and 69% were White, 22% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (47%), MTC (44%), and non-medullary thyroid carcinoma (5%).

Serious adverse reactions occurred in 33% of patients who received RETEVMO. The most frequent serious adverse reaction (in ≥2% of patients) was pneumonia. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Permanent discontinuation due to an adverse reaction occurred in 5% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation included increased ALT (0.4%), sepsis (0.4%), increased AST (0.3%), drug hypersensitivity (0.3%), fatigue (0.3%), and thrombocytopenia (0.3%).

Dosage interruptions due to an adverse reaction occurred in 42% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥2% of patients included ALT increased, AST increased, hypertension, diarrhea, pyrexia, and QT prolongation.

Dose reductions due to an adverse reaction occurred in 31% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included ALT increased, AST increased, QT prolongation and fatigue.

The most common adverse reactions, including laboratory abnormalities, (≥25%) were increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased platelets, increased glucose (22%; 0.7%), increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema, decreased glucose, rashes (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and diarrhea (0.7%).
Table 2: Laboratory Abnormalities (‡20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO¹</th>
<th>RETEVMO²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7</td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.6</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>35</td>
<td>0.1</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
</tr>
</tbody>
</table>

¹ Denominator for each laboratory parameter is based on the number of patients with a baseline value and post-treatment laboratory value available, which ranged from 671 to 692 patients.

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 10% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid concurrent use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally acting antacid).

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor decreases selpercatinib plasma concentrations, which may reduce RETEVMO anti-tumor activity. Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid concomitant administration of CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryo/fetal and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 10% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ⊳ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily), ½ of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (5 with short tail and one with small skull and localized edema at the neck and thorax).

Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the final dose.

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 06MAR2020

RETEVIMO™ (selpercatinib) capsules, for oral use

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Females and Males of Reproductive Potential
Based on animal data, RETEVMO can cause embryopathy and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO.

Contraception

Females
Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose.

Males
Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the final dose.

Infertility
RETEVMO may impair fertility in females and males of reproductive potential.

Pediatric Use
The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced RET fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications.

Animal Toxicity Data
In 4-week general toxicology studies in rats, animals showed signs of physical hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Mice also showed signs of mineral to marked increases in physical thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Geriatric Use
Of 792 patients who received RETEVMO, 34% (293 patients) were ≥ 65 years of age and 10% (67 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥65 years of age and younger patients.

Renal Impairment
No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease.

Hepatic Impairment
Reduce the dose when administering RETEVMO to patients with severe (total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment.

Rx only.
Additional information can be found at www.retevmo.com.

Lilly
Eli Lilly and Company, Indianapolis, IN 46209, USA
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SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use
Leveraging Immunotherapy Is Key for Improving Cervical Cancer Outcomes

by CAROLINE SEYMOUR

STANDARD-OF-CARE APPROACHES including chemotherapy and the use of bevacizumab (Avastin) maintain their position as beneficial treatment options for patients with cervical cancer. However, immunotherapy has begun to leave its mark in the first- and second-line treatment paradigm. Specifically, the FDA approval of pembrolizumab (Keytruda) and tisotumab vedotin-tftv (Tivdak) in 2021 have introduced much needed options for patients with metastatic or recurrent cervical cancer, respectively, according to Yovanni Casablanca, MD.

Integration of these agents in the first and second line were topics of discussion at the Society of Gynecologic Oncology (SGO) 2022 Annual Meeting on Women’s Cancer. In addition to the benefit each provides, Casablanca noted that testing and multidisciplinary care teams will play a large part in establishing a role for pembrolizumab and tisotumab vedotin.

“When you have recurrent or metastatic cervical cancer that’s not amenable to surgery or localized treatment with radiation, PD-L1 testing with the assessment of the combined positive score is important to get as soon as you can, so that you can decide on the appropriate first-line treatment regimen,” Casablanca said in an interview with OncologyLive®.

“Chemotherapy is not going away, and the use of bevacizumab [Avastin] is not going away, but [PD-L1 testing] will help you decide if you want to add pembrolizumab to that backbone. After first-line treatment, there are a lot of promising options in the second-line setting. We have other immune therapies that, hopefully, will be approved soon, possibly, without the need for PD-L1 positivity, although we’ll see what the FDA decides.”

Casablanca, a US Air Force lieutenant colonel, program director of the Fellowship in Gynecologic Oncology at the National Capital Consortium, and associate professor in the Department of Gynecologic Surgery and Obstetrics at the Uniformed Services University in Bethesda, Maryland, discussed the unique challenges presented with combination immunotherapy regimens and touched on the necessity of inclusive research with novel therapies.

What are the most notable challenges in the integration of pembrolizumab and tisotumab vedotin in clinical practice?

Since the last SGO Winter Meeting 2 years ago, there have been some breakthrough approvals from the FDA for use of new systemic treatment regimens in metastatic or recurrent cancer. One of those approvals is the addition of pembrolizumab to chemotherapy and bevacizumab in the first-line setting for cervical cancer based on data from the KEYNOTE-826 trial [NCT03635567].

For patients with metastatic and recurrent cervical cancer, the standard had been to utilize 2 chemotherapies and consider adding bevacizumab to it. That 3-drug regimen had been our standard 2 years ago. Now with the data from KEYNOTE-826, for patients who have PD-L1-positive tumors, we can add pembrolizumab to that regimen. The biggest change for clinicians is wrapping their head around using 4 drugs at the same time, potentially, to treat patients with metastatic or recurrent cervical cancer and getting PD-L1 biomarker testing as soon as this diagnosis is made so they can choose whether they’re going to add pembrolizumab [to that standard 3-drug regimen].

Another breakthrough was the approval of a new novel drug called tisotumab vedotin, which is an antibody-drug conjugate that is now approved in the second-line setting. The agent had remarkable duration of response, immediacy of the response, and overall survival [in the pivotal trial]. Compared with where we were 2 years ago, that’s a big improvement. Despite the challenges of the pandemic, there have been some breakthroughs and progress in the treatment of patients with metastatic and recurrent cervical cancer.

One of the things that was on community members’ minds, particularly with tisotumab vedotin, is that this class of medicine is associated with ocular adverse effects [AEs]. There is a need for partnership with an eye care professional such as an optometrist or an ophthalmologist with knowledge of these AEs when you use this drug in the second-line setting, which is not a very common relationship.

We don’t usually have our offices next door to an eye care professional. A lot of folks are not sure how they’re going to navigate and establish those relationships. There is an FDA box warning about the ocular AEs [TABLE 1].

Thankfully, we have a mitigation and management plan for these ocular eye AEs. Proactiveness and educating the patient on the importance of their eye care plan will help to make this, hopefully, not as big of an issue.

What are some of the disease-specific challenges of developing novel therapies for patients with cervical cancer?

Cervical cancer is a unique disease and patient population for us compared with endometrial and ovarian cancer. Metastatic and recurrent cervical cancer is not as common in our practice. [Cervical cancer] is not a very common disease overall, so that’s 1 challenge. One of the unique things about patients with cervical cancer is that they’re quite young overall. [Women with cervical cancer] are very young, otherwise healthy women, sometimes with...
families and children. It’s an important population, even though it’s a smaller population to focus on. The other thing that is important to highlight is that cervical cancer and advanced cervical cancer is a disease that is even a bigger burden and problem worldwide in underdeveloped countries or countries where preventive care is less robust.

A lot of the breakthroughs that we have in the United States may not be as applicable globally. It really is a very niche type of research that’s done with these advancements because it’s a smaller population with needs that vary from country to country. The population is very heterogeneous, too, even in the United States.

What therapeutic class has the most potential to make an impact on the paradigm?

With immune therapy and immunotherapy combinations—not just pembrolizumab-based combinations, but other immune therapy combinations, and novel immune therapy agents, such as TIL [tumor infiltrating lymphocyte] treatment—there is a growing amount of knowledge in the role of the immune system and the potential hope we have in immune therapy, not just as single agents, but in combination with standard regimens. I don’t think that the future of cervical cancer is going to hang on giving 1 drug at a time.

I think the future of cervical cancer treatment is going to be using combinations of multiple treatments to see improvement in survival.

What can be done to make sure these developments reach the community at large?

There are significant disparities in our country’s health care system. Cervical cancer patients have a vast demographic makeup with many cultural and racial ethnic backgrounds. By allowing and supporting clinical trial enrollment for every person and every population, we hope to improve the extension of these novel therapies to populations or subsets that normally wouldn’t have had access to them. There certainly is a lot of work to do to reach out to patients who are under- or noninsured and patients who don’t have the access to larger or tertiary medical centers with novel therapies available.

Is there any research you’re involved in that you’d like to highlight?

So much activity is going on now in cervical cancer trials across the country, including the addition of immune therapy to the chemoradiation backbone for locally advanced disease and looking at combinations of therapies. Now that patients are getting immune therapy in the first-line setting: What do we do with immune therapy if they progress and need something in the second-line setting? Should patients get immune therapy again? Should we switch classes? How do we make immune therapy effective and tolerable at the same time?

The trial that I’m involved in in the cervical cancer field is looking at adding triapine, which is a novel drug, to the backbone of chemotherapy and radiation in locally advanced cervical cancer.

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TABLE. Pivotal Approvals for Patients With Cervical Cancer¹,²

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab (n = 273)</th>
<th>Placebo (n = 275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (19.8-NR)</td>
<td>16.3 (14.5-19.4)</td>
</tr>
<tr>
<td>HR, 0.64; 95% CI, 0.50-0.81; P = .0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>10.4 (9.7-12.3)</td>
<td>8.2 (6.3-8.5)</td>
</tr>
<tr>
<td>HR, 0.62; 95% CI, 0.50-0.77; P &lt; .0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective response rate</td>
<td>68% (62%-74%)</td>
<td>50% (44%-56%)</td>
</tr>
<tr>
<td>Median DOR, months (range)</td>
<td>18.0 (1.3-24.2)</td>
<td>10.4 (1.5-22.0)</td>
</tr>
</tbody>
</table>

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**Boxed warning**

**Ocular toxicity:** Tisotumab vedotin can cause changes in the corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss, and corneal ulceration.

- Conduct ophthalmic exams including visual acuity and slit lamp exam at baseline, prior to each dose, and as clinically indicated.
- Adhere to premedication, including topical corticosteroid eye drops and topical vasoconstrictor drops, and required eye care before, during and after infusion.
- These include the use of cooling eye packs during infusion and topical lubricating eye drops for the duration of therapy and 30 days following treatment.
- If severe symptoms occur withhold treatment until improvement and resume, reduce the dose, or permanently discontinue, based on severity.

---

**References**

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

**ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE**

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial\(^1-3\)

**IMPORTANT SAFETY INFORMATION**

**DARZALEX® AND DARZALEX FASPRO®:**

**CONTRAINDICATIONS**

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

**DARZALEX®: Infusion-Related Reactions**

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, and pulmonary edema.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and anxiety. Less common symptoms were wheezing, allergic rhinitis, fever, chest discomfort, pruritus, and hypotension.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate medical management.
DARZALEX® reported with daratumumab-containing products, including systemic administration-related reactions that can occur with DARZALEX® or life-threatening reactions, and local injection-site reactions. Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

**Administration Reactions**

Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**Efficacy in long-term follow-up**

At median ~5 years (56 months)² of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.²

- **53% of patients had not progressed** after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)³

  - 47% reduction in the risk of disease progression or death with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

  - These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

**Safety results in long-term follow-up**

At median ~5 years of follow-up²,³:

- Most frequent TEAEs ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms

  - Grade 3/4 infections were 41% for DRd vs 29% for Rd

  - Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and citalacta (11% vs 11%)

  - These ~5-year analyses are not included in the current Prescribing Information.

**Powerful efficacy to start the treatment journey**¹,⁴

After a median ~30 months of follow-up, mPFS was not reached with DARZALEX® + Rd vs 31.9 months with Rd alone.¹,⁴

- **70.6% of patients had not progressed** with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)³

  - 44% reduction in the risk of disease progression or death with DRd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; P<0.0001)

**Demonstrated safety profile**

**MAIA Study Design**: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.¹

<table>
<thead>
<tr>
<th><strong>CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR=injection-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range: 0.0-41.4 months.4</strong></td>
</tr>
<tr>
<td><strong>Range: 0.03-69.52 months.3</strong></td>
</tr>
<tr>
<td><strong>TEAEs are defined as any adverse event (AE) that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered drug related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.</strong></td>
</tr>
<tr>
<td><strong>Range: 0.0-41.4 months.4</strong></td>
</tr>
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</tr>
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| **MAIA Study Design**: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.¹

**See the latest data rolling out. Visit FrontlineMomentum.com**

emergeny care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

DARZALEX FASPRO®: Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

**Systemic Reactions**

In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**

With an ~3 to 5 minute subcutaneous injection, DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab.

FASPRO®: Hypersensitivity and Other Administration Reactions

**Systemic Reactions**

In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**

FASPRO®: Hypersensitivity and Other Administration Reactions

**Systemic Reactions**

In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE**
Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed [defined as occurring the day after administration] systemic administration-related reactions.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 3.5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

DARZALEX® and DARZALEX FASPRO®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

DARZALEX® and DARZALEX FASPRO®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman, DARZALEX® and DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX FASPRO® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX FASPRO® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are: neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia. The most common hematologic laboratory abnormalities (≤40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with thalidomide and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.

References:
DARZALEX® (daratumumab) injection, for intravenous use

**INDICATIONS AND USAGE**
DARZALEX is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

**CONTRAINDICATIONS**
DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation (see Warnings and Precautions).

**WARNINGS AND PRECAUTIONS**

### Infusion-Related Reactions
DARZALEX can cause severe or life-threatening infusion-related reactions, including anaphylactic reactions. These reactions can be managed with supportive care and treatment of the underlying disorder. In clinical trials (monotherapy and combination: N=2,068), infusion-related reactions occurred in 37% of patients with the Week 1 16 mg/kg infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had Grade 3/4 infusion-related reaction to Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 72 hours). The incidence of infusion modification due to infusion-related reactions was 40% (median: 0.9% of 16 mg/kg infusions for the first infusion, 14% for Week 2, and subsequent infusions were approximately 4, 7, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours post-dose. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, dyspnea, cough, as well as hypertension and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension (see Adverse Reactions).

When DARZALEX dosing was interrupted in the setting of ASTC (CASSIOPEIA) for a median of 3.76 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASTC. Infusion-related reactions occurring at re-initiation of DARZALEX following ASTC were consistent in terms of symptom and severity (Grade 3 or 4) or with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULES, patients receiving combination treatment (N=97) were administered the first 16 mg/kg dose at Week 1 split over two days, In total, 15% of patients experienced infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.2 to 14.2 hours). The incidence of infusion-related reactions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion (see Dosage and Administration (2.3) in Full Prescribing Information). Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusate rate when re-starting the infusion (see Dosage and Administration (2.4) in Full Prescribing Information). To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions (see Dosage and Administration (2.3) in Full Prescribing Information). Patients at a history of chronic obstructive pulmonary disease may require additional post-injection medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for moderate to severe chronic obstructive pulmonary disease (see Dosage and Administration (2.3) in Full Prescribing Information).

**Interference with Serological Testing**
Daratumumab binds to both CD38-positive and CD38-negative B cells (BCBs) and results in a positive Indirect Antibody Test (Indirect Coombs test). Daratumumab-mediated positive indirect antibod test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum (see Adverse Effects). The detection of a patient’s ABO and RH blood type are not impacted (see Drug Interactions).

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX (see Dosage and Administration (2.1) in Full Prescribing Information).

**Neutropenia**
DARZALEX may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

**Thrombocytopenia**
DARZALEX may increase thrombocytopenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with thrombocytopenia for signs of infection. Consider withholding DARZALEX until recovery of thrombocytes.

**Table 1: Adverse Reactions Reported in ≥10% of Patients and With a Least a 5% Frequency in the Rd Arm in MAIA**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>67</td>
<td>7</td>
<td>0 &lt;1</td>
<td>0</td>
<td>46</td>
<td>&lt;1</td>
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<tr>
<td>Constipation</td>
<td>41</td>
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<td>0</td>
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<td>0</td>
<td>36</td>
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<tr>
<td>Nausea</td>
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<td>0</td>
<td>0</td>
<td>23</td>
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<tr>
<td>Vomiting</td>
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<td>Infections</td>
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<td>General disorders and administration site conditions</td>
<td>Infusion-related reactions</td>
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<td>0</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paresthesia</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucous membrane and respiratory disorders</td>
<td>Mucositis</td>
<td>24</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>13</td>
<td>0</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Key: D-daratumab, Rd-lenalidomide-dexamethasome.

**Table 2: Treatment-Emergent Hematologic Laboratory Abnormalities in MAIA**

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>DRd (N=364)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>90</td>
<td>30</td>
<td>5</td>
<td>0</td>
<td>82</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>91</td>
<td>39</td>
<td>17</td>
<td>0</td>
<td>77</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>94</td>
<td>31</td>
<td>6</td>
<td>0</td>
<td>57</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>67</td>
<td>6</td>
<td>3</td>
<td>&lt;1</td>
<td>58</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Key: D-daratumab, Rd-lenalidomide-dexamethasome.

**Released/Refractory Multiple Myeloma**
Combination Treatment with Lenalidomide and Dexamethasone

**Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Frequency in the DRd Arm in POLLUX**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRd (N=283)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>Respiratory tract infection</td>
<td>48</td>
<td>6</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>35</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>43</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the ORAL in POLLUX (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Daratumumab (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Cough</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizzinessa</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Hematologic Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>95%</td>
<td>42%</td>
<td>0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52%</td>
<td>36%</td>
<td>7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>52%</td>
<td>13%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

* Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Immunogenicity

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with daratumumab. In the combination studies, hepatitis B virus reactivation also occurred in 1% of patients treated with daratumumab in monotherapy. daratumumab has the potential to cause reactivation of hepatitis B virus, and patients with or without a history of hepatitis B virus infection should be carefully monitored for evidence of reactivation.

Fetal/Neonatal Adverse Reactions

Daratumumab can cause fetal harm when administered to a pregnant woman. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women. There is no available data on the use of DEX with daratumumab in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

In the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women. There is no available data on the use of DEX with daratumumab in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women. There is no available data on the use of DEX with daratumumab in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women. There is no available data on the use of DEX with daratumumab in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

**INDICATIONS AND USAGE**

DARZALEX FASPRO® is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

**CONTRAINDICATIONS**

DARZALEX FASPRO® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation (see Warnings and Precautions and Adverse Reactions).

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity and Other Administration Reactions**

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO (see Adverse Reactions).

**Systemic Reactions**

In a pooled safety population of 822 patients with multiple myeloma (N=439) or light chain (AL) amyloidosis (N=383) who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone (VCD, N=363) or in combination with bortezomib, cyclophosphamide and dexamethasone plus thalidomide (VCDThalif, N=359), 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 4% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with all subsequent injections. The median time to onset was 2.3 hours (range: 9 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of patients.

**Local Reactions**

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 4.8%. The most frequent (≥1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5.5 minutes (range: 0 minutes to 6.3 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

**Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis**

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone (VCD). Serious cardiac adverse reactions occurred in 16% and fatal cardiac adverse reactions occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied. Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

**Neutropenia**

Daratumumab may increase neutropenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

**Thrombocytopenia**

Daratumumab may increase thrombocytopenia induced by background therapy (see Adverse Reactions). Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.5) in Full Prescribing Information).

**Interference with Determination of Complete Response**

Interference with determination of complete response and of disease progression can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

**ADVERSE REACTIONS**

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

- Hypersensitivity and Other Administration Reactions (see Warning and Precautions).
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis (see Warning and Precautions).
- Neutropenia (see Warning and Precautions).
- Thrombocytopenia (see Warning and Precautions).

**Clinical Trials Experience**

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

**Relased/Refraayl Multiple Myeloma**

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of 9 patients enrolled in PLEIADES (see Clinical Studies (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=45) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in <5% of patients included pneumonia, influenza, and diarrhea. Fatal adverse reactions occurred in 3% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in combination with lenalidomide and dexamethasone included: fever, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

**Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis**

Infections:

- Upper respiratory tract infection
- Pneumonia
- Bronchitis
- Urinary tract infection

**Musculoskeletal and connective tissue disorders**

- Muscle spasms
- Back pain

**Respiratory, thoracic and mediastinal disorders**

- Dyspnea
- Cough

**Musculoskeletal and connective tissue disorders**

- Muscle spasms
- Back pain

**Respiratory, thoracic and mediastinal disorders**

- Dyspnea
- Cough

**Nervous system disorders**

- Peripheral sensory neuropathy
- Psychiatric disorders

- Hypertycemia
- Hypocalcemia

**Metabolism and nutrition disorders**

- Fatigue
- Anemia

**Immunogenicity**

- Drug interactions
- Lab abnormalities

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.
In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of patients developed treatment-emergent anti-daratumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 1% of patients developed treatment-emergent anti-HuPo20 antibodies. The anti-HuPo20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-HuPo20 antibodies tested positive for neutralizing antibodies.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see Warnings and Precautions].

Advise patients that daratumumab can affect the results of some tests used to determine complete response [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see Warnings and Precautions].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [see Warnings and Precautions].

Cardiac Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

DRUG INTERACTIONS

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

Patient Nonadherence

Interference with Laboratory Tests

Advise patients that daratumumab can affect the results of some tests used to determine complete response [see Clinical Pharmacology (12.3) in Full Prescribing Information].

When combining DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 31% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients.

Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, diarrhea, cough, dyspepsia, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients.

Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3)] in Full Prescribing Information].

INTERFERENCE WITH LABORATORY TESTS

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

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: tachy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see Warnings and Precautions].

Asthma

Advise patients to contact their healthcare provider if they have asthma [see Warnings and Precautions].

Caucasian Use

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

Immune System: Anaphylactic reaction, systemic administration reactions (including death)

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 1% of patients developed treatment-emergent anti-daratumab antibodies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Investigators Tackle the Untapped Potential of Personalized Medicine

by BRITTANY LOVELY

A study at the 2021 American Society of Clinical Oncology Annual Meeting, specific to clinicians treating patients with non–small cell lung cancer, showed that they were testing for only 1 marker as opposed to using a broader panel.² What has been your experience in seeing the shift from testing for single markers to using broader genomic panels in practice?

It’s a very interesting topic to discuss because I think most people understand what personalized medicine is, but basically, it’s just tailoring the treatment toward the individual patient. And I think the field of cancer, especially, has focused on tailoring treatment to the individual patient. We’re looking at very targeted drugs, [which require a] very specific test, as you had mentioned. I think that is probably because immunotherapy is the hottest wave of therapy for nearly 10 years at this point and we rely, at least right now, on markers such as PD-L1 expression, the major target for a lot of checkpoint inhibitors.

[However,] it’s just 1 marker. We know that a tumor or cancer is made up of many, many different interactions from the immune milieu or the immune cells that are around the cancer, the tumor metabolic environment. That could involve different protein interactions or the epigenetic environment that could lead to some of these different proteins [being involved]. There are all these different factors that could [inform you to] look at different markers.

That’s where we’re headed now: We’re trying to expand beyond a one-marker-fits-all [approach]. These markers will be a magic shoe that fits [a certain patient] and will predict outcomes or predict response to a drug. But it’s going to take more than that because we know there are so many other different measurable markers that we can now look for with different technologies that are available to us, and investigators are looking for more and more.

What steps are being taken to build that information base and what information is showing the most promise across tumor types?

At John Theurer we are interested in pushing the field forward, looking at [this information from] more of a research perspective to try and discover newer biomarkers or newer combinations of therapies that would show a better response based on [results of] the testing we run. That includes more targeted genomic mutation panels. We work with a company called the Genomic Testing Cooperative [and] we have an in-house laboratory now. For me, specifically as a lymphoma specialist, I can test for up to 400 targeted molecular mutations as well as chromosomes to [assess] the genomic structural operations on the chromosomes, which can be detected as well.

We can look at things such as cell-free DNA [and] cell-free RNA sequencing, and monitor patients for detection of these potential cancer signatures or cancer biomarkers. It is a very fascinating field because there are ways that we don’t know yet on how a patient will respond [based on this information].

Another big thing at Hackensack [Meridian Health] and the cancer center, is that we have a very strong, scientific bench looking at the microbiome. That has really hit the news lately as investigators can predict response or predict relapse of different cancer types just by looking at the stool environment, which is interesting because no one would have thought about that 20 years ago, but it makes a lot of sense because every gastrointestinal tract has its own microbiome or bacterial signature.

That plays a huge interaction with the amount of inflammation a patient may have in their body, their immune status—how their body will monitor, detect, or destroy circulating cancer cells that are remaining. This is important for [patients with] stomach or colon cancers, but also could affect those who require bone marrow transplant. Investigators are using the microbiome to predict GVHD [graft-vs-host disease], which is just this phenomenon of the bone marrow transplant attacking the patient.
trying to look at the available combination of drugs for multiple myeloma and sort out how to correctly sequence them.

Lastly, I’ll say that with a lot of these newer biomarker monitoring or detection tools, measurable residual disease or MRD detection comes into play. By using liquid biopsies or targeted genomic mutation testing for the patients who are maybe precancerous or at high risk of developing cancer, can you predict whether they will develop cancer?

That’s huge. Many individuals may have at least 1 risk for cancer—whether it’s a family member who received a diagnosis or some kind of environmental exposure—individuals want to know if they will develop breast or lung cancer in their life. Answering those questions is part of our vision or goal the data we are trying to leverage.

On the same spectrum for patients who are cured, or 5 years out, or maybe just finished their treatment and they’re in remission—how can we improve their outcomes in the time after they have completed their treatment? That may include using data from their socioeconomic background or their physical wellness or metabolic risk factors, such as obesity. All these factors affect a patient’s survivorship spectrum.

We’re also looking to prevent cardiovascular risk later in their life from their treatments or prevent cancer from coming back as well. There are late toxicities from our treatments. The post-cancer treatment spectrum is an untapped field.

**With access to all these data, what are the hurdles preventing integration of the information to clinical practice?**

It is easy to address the disadvantages of too much data at a clinician’s fingertips. In 2020, there were over 60 cancer drug approvals. That number is going to keep growing. Just looking at the number of drugs that are available for a community oncologist, there are hundreds of possible options, not to mention the combinations. As the possibilities start to exponentially grow and it becomes more and more difficult for a smaller practice or community-based oncology practice to keep up with all of these new drugs.

On top of that you have conferences with new updates or published journal articles, and these can encompass many different types of information, not just randomized clinical trial data, but new information on genomic mutations or different molecular targets. These data really stretch an oncologist’s mind because these are targets that the general oncologist may not have thought of or only learned in medical school many, many years ago.

Now you have to really understand it and learn it, because if you are going to prescribe certain agents, you have to know what they are doing; you have to be educated. The quantity of data can be a really big disadvantage. Looking for the quality of the data can be hard as well because there are so many sources of information that must be vetted.

There are advantages. You could look at the flip side, which is that the more options that are available for your patient, the better the outcome can be. You have more lines of therapies you could integrate into the rotation if they fail or progress after 1 or 2 or 3 prior lines. You could choose targeted drugs to tailor a patient’s treatment. All that information helps, and I think it’s better for the patient. It’s just a disadvantage for the treating team because they have to synthesize and ingest all of that information.

**MORE FROM John Theurer Cancer Center**

**Feldman on Adding Etoposide to Brentuximab Vedotin/CHP in Peripheral T-Cell Lymphomas**

Tatyana Feldman, MD, hematologist and medical oncologist, John Theurer Cancer Center, discusses the efficacy of adding etoposide to brentuximab vedotin (Adcetris) plus CHP (cyclophosphamide, doxorubicin, and prednisone) followed by brentuximab vedotin consolidation in patients with newly diagnosed, CD30-expressing peripheral T-cell lymphomas. Feldman provides an overview of data from a phase 2 trial (NCT03113500) presented at the 63rd American Society of Hematology Annual Meeting and Exposition, which showed that the 18-month progression-free survival rate was 61% with this approach for all patients.

TO WATCH, scan the QR code or visit bit.ly/30qR3lh.

**Goy on the Utility of Axi-Cel and Brexu-Cel in Relapsed/Refractory NHL**

Andre H. Goy, MD, physician in chief, Hackensack Meridian Health Oncology Care Transformation Service; chairman & chief physician officer, John Theurer Cancer Center; Lydia Pfund Chair for Lymphoma, Academic Chairman Oncology, Hackensack Meridian School of Medicine; and professor of medicine, Georgetown University, discusses the updated clinical data from the phase 2 ZUMA-5 trial (NCT03105336) of axicabtagene cilo-leucel (axi-cel; Yescarta) in patients with relapsed or refractory indolent non-Hodgkin lymphoma (NHL) and real-world findings with brexucabtagene autoleucel (brexu-cel; Tecartus) in mantle cell lymphoma.

TO WATCH, scan the QR code or visit bit.ly/3gLQqA.

**McCloskey on the Utility of Decitabine Plus Cedaazaridine in Lower-Risk MDS**

James K. McCloskey, MD, chief, Leukemia Division, John Theurer Cancer Center, Hackensack Meridian Health, discusses the utility of decitabine plus cedaazaridine (Inquiva) in lower-risk myelodysplastic syndromes (MDS), based on data from the long-term follow-up of the phase 3 ASCERTAIN trial (NCT03306264). Data presented at the 63rd American Society of Hematology Annual Meeting and Exposition showed that patients had an overall response rate of 56.5% with the combination. McCloskey also discussed the rate of transfusion independence, which was an important achievement in this population.

TO WATCH, scan the QR code or visit bit.ly/3rtUQG1.
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**OCM Successes Highlighted in COA Survey, Bolstering Support for Continuation**

by MARY CAFFREY

**THE ONCOLOGY CARE MODEL** (OCM) is set to expire on June 30, 2022. With no successor on the horizon, features such as dedicated navigators and weekend appointments could be reduced or lost, said respondents to a recent survey by the Community Oncology Alliance (COA). The survey results show that for those participating in the OCM—CMS’ alternative payment model in cancer care—respondents said that the program has succeeded in reducing costs and improving patient outcomes.

With the end date set, practices may be forced to reduce or cease the program’s most popular and successful features if revenues that supported them are eliminated. “Overall, practices indicated that the OCM transformed the patient experience for the better by comprehensively addressing patient needs and disparities,” according to a news release from COA.

CMS’ Center for Medicare & Medicaid Innovation (CMMI) launched the OCM in 2016 to run over 5 years. This gave participating practices tools and funds to reinvent cancer care delivery with an emphasis on coordinating care, preventing unnecessary trips to the emergency department, offering survivorship care, and managing the cost of therapies. The program was originally set to run through 2021 but was extended for a year because of the COVID-19 pandemic.

A key feature of the program is the **Monthly Enhanced Oncology Services (MEOS)** payment, which funds the extra services that practices offer under the program. This payment is triggered by each cancer episode at the practice. Other program funds involve more extensive reporting requirements.

Of the 126 practices participating in the OCM in July 2021, 83 responded to COA’s survey and 73 are still participating. The results reflect feedback from the 51 practices that completed the entire survey. Participants were asked how the OCM affected cancer care, whether they would continue in the model, and whether they expected reductions in service when the model ended.

In other analyses of the OCM, the initiative received high marks for improving patient experience, but practices needed time to learn to fully implement the model. As the rise of immunotherapy unfolded during the model’s implementation, practices struggled to make parts concerning financial savings work because pricing assumptions often failed to keep pace with cancer innovation. Still, many oncologists said they would not want to revert to delivering care without navigators, care planning, or survivorship services, and many larger practices have taken steps to figure out how to offer these services post OCM.

**FIGURE. Survey Results Favor OCM Continuation from Community Oncologists²**

Survey participants (N = 55)

**EFFECT OF OCM**

Scale 1-100
(0 – no effect, 100 – tremendous effect)

- Patient experience: 62
- Operational efficiencies: 56
- Consistency in cancer treatments: 56
- Consistency on cancer treatments: 49
- Consistency on cancer treatments: 45

**Would you continue in the OCM if financial support in the form of MEOS payments were reduced or eliminated:**

- Yes, as it is currently operating, with full MEOS payments
- Yes, even if MEOS payments were reduced by half
- Yes, willing to continue without any MEOS payments

MEOS, monthly enhanced oncology services; OCM, Oncology Care Model.

**STRONG EFFECT ON PATIENT EXPERIENCE**

Respondents to the COA survey were asked to use a scale of 0-100, with 0 having no effect and 100 having a tremendous effect, to evaluate the OCM in 5 categories: patient experience, operational efficiencies, consistency in cancer treatments, reduced total cost of care, and addressing health disparities.

Average responses for all categories showed that the OCM has had positive effects: patient experience (62), operational efficiencies (56), consistency in cancer treatments (56), consistency on cancer treatments (49), and consistency on cancer treatments (45).
experience, 62; operational efficiencies, 56; consistency in cancer treatment, 56; reduced total cost of care, 49; and addressing disparities, 45 (FIGURE).2

**FUTURE OF MEOS PAYMENTS IS KEY**
The survey asked practices if they would continue in the OCM, and whether that would change if financial support in the form of MEOS payments were reduced or eliminated:
- 84% would continue in the OCM as it is currently operating, with full MEOS payments.
- 80% would continue even if MEOS payments were reduced by half.
- 27% would be willing to stay in the OCM without any MEOS payments.

Practices were given the chance to give open-ended comments on what the end of the OCM would mean to patients. Many said that staff now considered an essential part of the care routine would be reassigned or lost, such as through reassignments of lay navigators or program coordinators or the end of weekend hours that help prevent overuse of the emergency department.

Regarding service reductions at the end of the OCM, the average response indicated that practices might reduce key positions such as care planner, survivorship planner, and nurse navigator by roughly 25%.

**SURVEY PARTICIPANTS WANT AN OCM SUCCESSOR**
The survey participants expressed disappointment that CMMI has no plans for a successor to the OCM in place. In 2019, a plan called Oncology Care First was proposed, but it was delayed because of the COVID-19 pandemic and its future is unknown.

CMMI has a duty to shepherd ongoing oncology reform, given the investment that practices have made, according to Bo Gamble, COA’s director of strategic practice initiatives. “The OCM led the way for a transformation in the delivery of cancer care, as well as a mindset for continual quality improvement with emphasis on efficiency and value. There will be a void in leadership if CMMI steps away from this important work.”

Prior to the survey results, COA had written several letters in support of the continuation of the OCM. Target action items of concern included virtual meetings to discuss the benefits of the OCM and navigate a pathway forward. The letter addressed to CMS and CMMI in November 2021 requested that the OCM deadline be extended to at least December 2022.

FOR MANY SMALL PRACTICES, creating a budget is an annual exercise that culminates in a binder that sits on the shelf and collects dust for the remainder of the year. But experts say practices that don’t develop and regularly review a budget are missing out on a tool that can provide warning signs of financial trouble and fraud, and help to make large purchases less disruptive to cash flow.

“If you think of a practice as a living body, the budget is like a vaccine,” said Rick Gundling, CMA, senior vice president for healthcare financial practices for the Healthcare Financial Management Association. “Having one doesn’t mean your practice’s health won’t go off track, but the risks are minimized. And when you check in on a periodic basis, that’s like your financial stethoscope.”

**Creating a better budget**
An effective budget does not have to be complicated but it should be designed to match the management style of the physician or else it won’t be effective, according to experts.

Physicians who prefer high-level overviews with minimal details of the business should work from budgets with those same traits. Doctors who are detail-oriented may be interested in a budget with more line items that show expenses in greater detail, said Cindy Nyberg, CPA, chief financial officer and strategic planning consultant for Fulcrum Strategies, a physician consulting firm in Raleigh, North Carolina. For example, medical supplies could be one broad category or broken down into specific subcategories for greater detail.

Melissa Lucarelli, MD, a primary care physician in Randolph, Wisconsin, tried a detailed annual budgeting process but didn’t see any return on the time and cost involved in creating it. “For a small practice like mine, I don’t have the luxury of saying, ‘We’ll go into the red this month and make it up next month,’” she said.

What works for her practice is a simpler accounting review of monthly expenses compared with what the practice has spent in the past. “We are just looking at how much we have, how much we are getting in, and how much we need to pay each month,” said Lucarelli, a member of the Medical Economics editorial advisory board. “To me, it feels more agile and less stressful.” Lucarelli’s strategy for budgeting illustrates the best approach—find out what works.

“I always caution physicians to keep it as simple as possible,” said Nick Fabrizio, PhD, a principal at the Medical Group Management Association. “Come up with a simple process you can use that monitors revenue and expenses. It’s OK to forget things when you start. It’s better to do that than to create an elaborate budget with 50 line items that is too difficult to understand and becomes this big, scary thing that no one wants to touch.” Detail may be great, but keep in mind that more detail also requires more staff time to track, he added.

The first step in creating a budget is to look at revenue and payer mix, according to Nyberg. This will not only establish a starting point but offer insight into creating growth. “You can’t just say you’re going to increase revenue 10% next year,” she said.

Once revenue has been established in the budget, Nyberg suggested that expenses be organized and divided into categories such as occupancy, furniture and equipment, medical, miscellaneous, midlevel-provider, and physician, as well as supporting staff compensation and benefits. These broad categories make a budget much easier to understand, and if variances occur, more detailed information can then be gathered to give the physician a better idea of what is driving the change.

**Using a budget to improve a practice**
Once the budget has been created, it must be reviewed at least monthly to be useful. Gundling said physicians should look for trends by comparing the numbers with the prior month and with the same month from the previous year. If a particular category is much higher or lower than it was before, start asking questions.

“Once you understand the variance, then you can start formulating what to do,” Gundling said. “The budget causes you to ask the ‘what’ and the ‘why’ questions. It gives you more impetus to dig deep.”

Burns said that the budget in her practice acts as a guide on where to focus cost-cutting efforts. It can also be used to forecast returns on larger investments. When a budget is done correctly and regularly reviewed, it can offer many beneficial insights into the financial health—present and future—of a practice.
Unprecedented Advances Fuel Progress in the Treatment of AL Amyloidosis

by JACK KHOURI, MD

LIGHT-CHAIN (AL) AMYLOIDOSIS is a rare plasma cell disorder that involves the production of a misfolded amyloidogenic light chain by a plasma cell clone that deposits in various organs leading to organ failure. Traditionally, the treatment paradigm has focused on eliminating the culprit plasma cell clone with autologous hematopoietic cell transplantation (AHCT) in eligible patients or with bortezomib (V; Velcade)-based therapy (typically in combination with cyclophosphamide and dexamethasone [VCd]) in AHCT-ineligible patients. The goal of therapy for patients with AL amyloidosis is to achieve a swift and deep hematologic response which correlates with survival and organ function improvement.1 Therapeutic efforts have pivoted on implementing novel strategies that generate the deepest hematologic response, as well as targeting amyloid fibrils for immune destruction by means of anti-amyloid monoclonal antibodies in the hopes of reversing organ dysfunction.

ANDROMEDA OPENS THE DOOR

Daratumumab (Dara; Darzalex) is a human IgG1k anti-CD38 monoclonal antibody that is approved for the treatment of newly diagnosed and relapsed multiple myeloma. CD38 is abundantly expressed on plasma cells in patients with AL amyloidosis drawing attention to Dara as an attractive therapeutic means. Dara showed significant efficacy in small case series in relapsed AL amyloidosis with response rates of 70% to 80%.2,3 The pivotal phase 3 ANDROMEDA study (NCT03201963) assessed the effect of the addition of Dara to the standard of care VCd in patients with newly diagnosed AL amyloidosis.4 The study enrolled all patients with AL amyloidosis except for those with advanced Mayo 2004 stage IIIIB patients (troponin ≥ 0.035 mcg/L and NT-proBNP ≥ 8500 ng/L).

Patients were randomized to 6 cycles of VCd with or without daratumumab and hyaluronidase-human-fih (Darzalex Faspro) followed by maintenance Dara for 2 years in the Dara arm. The primary end point was overall complete hematologic response (CR) rate. Major organ deterioration progression-free survival (MOD-PFS) was a secondary end point which was a composite end point that included end-stage renal or cardiac failure, hematologic progression, and death. The study enrolled 338 patients with the majority having cardiac involvement (71%) and over a third having advanced cardiac disease (stage IIIA, 36%). After a median follow-up of 11.4 months, the results were intriguing. More than half of patients who received Dara-VCd (n = 195) achieved hematologic CR (53%; 95% CI, 46.1%-60.0%) vs 18% (95% CI, 13.0%-24.3%) of those who received VCd alone (n = 193; odds ratio [OR], 5.1; 95% CI, 3.2-8.2; P < .001).5

Additionally, the deep responses occurred rapidly with a median time to CR of 60 vs 85 days, respectively. These results were confirmed in an update presented at 2021 American Society of Clinical Oncology Annual Meeting5 (FIGURE 1). The 6-month organ responses doubled with the quadruplet regimen (cardiac, 42% vs 22%; and renal, 53% vs 24%). The MOD-PFS composite end point was significantly better in the quadruplet arm (HR, 0.58) and the median time to next treatment was not reached vs 10.4 months in the VCd arm. Longer follow-up is needed for OS data to mature.6

All the adverse events (AEs) seen in this study were in line with prior experience with VCd and Dara. Serious adverse events occurred more frequently in the quadruplet arm (43%) vs 36% in the VCd arm but treatment discontinuation was a rare occurrence (4% in both arms). AEs also tended to abate once patients were switched to maintenance Dara. Dara administration-related reactions occurred in only 7% of the patients and were of low grade.4

WHAT’S NEXT FOR AL AMYLOIDOSIS

The results of the ANDROMEDA study supported the FDA approval of the quadruplet of Dara-VCd for the treatment of AL amyloidosis in January 2021 which constitutes the first FDA approval for this patient population. An ongoing phase 2 study (NCT04131309) is examining the role of Dara monotherapy in patients with stage IIIB AL amyloidosis who were excluded from ANDROMEDA. Organ responses in AL amyloidosis tend to be slow with a median time to response of 10.4 months and many patients continue with irreversible organ damage and poor quality of life despite achieving a deep hematologic response.7 Thus, targeting the amyloid fibril has been the focus of clinical trials in order to restore organ function and improve prognosis. Birtamimab (NEOD001) is a first in class humanized IgG1 which ensures clearance of deposited amyloid fibrils by phagocytosis. It showed improved organ responses in initial studies, but further development was interrupted in 2018 after the phase 2b PRONTO study (NCT02632786) did not meet its primary and secondary end points.8 Post hoc analyses of the randomized, double-blinded, placebo-controlled phase 3 VITAL study (NCT02312206) later found survival benefit for patients with advanced Mayo stage IV AL amyloidosis who received the study drug, leading to the return of birtamimab. The phase 3 AFFIRM-AL (NCT04973137) study is currently enrolling patients with Mayo stage IV AL amyloidosis.

CAEL-101 (11-1F4) is an amyloid-fibril reactive IgG1 monoclonal antibody that was found to be efficacious and without significant toxicity in the initial phase 1 study.9 The phase 2 dose selection study conducted at our center confirmed the safety profile of CAEL-101 and reported organ responses in all evaluable patients with renal AL amyloidosis. It also recommended 1000 mg/m2 as the phase 3 dose in combination with VCd.10 Updated organ responses in 18 patients were presented at the 56th American Society of Hematology annual Meeting and Exposition and also included patients who received Dara in combination with VCd. The results were intriguing with organ responses seen in all 9 evaluable patients with renal involvement and 6 of 11 evaluable patients with cardiac involvement.11 Two ongoing randomized phase 3 studies are studying CAEL-101 in advanced AL amyloidosis (stages IIIA and IIIB).
in combination with plasma-cell directed therapy (NCT04512235, NCT04504825).

We are seeing an unprecedented progress in the treatment of AL amyloidosis. Given the marked improvement in hematologic responses seen with the implementation of frontline daratumumab, the role of AHCT needs to be redefined especially its utility and timing. Anti-amyloid therapies are emerging as promising options to reverse organ damage and improve patients’ survival and quality of life. They will likely be included in the treatment paradigm of AL amyloidosis as clinical data continue to mature.

**FIGURE. Outcomes in the ANDROMEDA Study**

<table>
<thead>
<tr>
<th></th>
<th>Dara-VDd (n = 195)</th>
<th>VCd (n = 193)</th>
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</thead>
<tbody>
<tr>
<td>ORR (n = 195)</td>
<td>92%</td>
<td>77%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>79%</td>
<td>77%</td>
</tr>
<tr>
<td>CR</td>
<td>53%</td>
<td>50%</td>
</tr>
<tr>
<td>VGPR</td>
<td>25%</td>
<td>31%</td>
</tr>
<tr>
<td>PR</td>
<td>13%</td>
<td>26%</td>
</tr>
</tbody>
</table>

CR, complete response; Dara-VDd, daratumumab plus bortezomib with cyclophosphamide and dexamethasone; ORR, overall response rate; PR, partial response; VCd, bortezomib with cyclophosphamide and dexamethasone; VGPR, very good partial response.

**REFERENCES**


ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this

*Study design: Phase 2 open-label, single-arm trial (N=145) to evaluate the efficacy and safety of ZYNLONTA as a monotherapy in r/r DLBCL after 2 or more systemic therapies. Patients received 0.15 mg/kg Q3W for 2 cycles with dexamethasone premedication (unless contraindicated), then 0.075 mg/kg Q3W for subsequent cycles. Primary endpoint was ORR, evaluated by independent review committee using Lugano 2014 criteria. ZYNLONTA was administered until progressive disease or unacceptable toxicity.1

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Effusion and Edema Serious effusion and edema occurred. Grade 3 edema: 3% (primarily peripheral edema or ascites); Grade 3 pleural effusion: 3%; Grade 3/4 pericardial effusion: 1%. Monitor patients for new/worsening edema or effusions. Withhold ZYNLONTA for Grade ≥2 until toxicity resolves. Consider diagnostic imaging in patients with symptoms of pleural or pericardial effusion, such as new/worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management.

Myelosuppression Serious or severe myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 32%; thrombocytopenia: 20%; anemia: 12%. Grade 4 neutropenia: 21%; thrombocytopenia: 7%. Febrile neutropenia occurred: 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA.

Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Infections Fatal and serious infections, including opportunistic infections, occurred. Grade ≥3: 10%; fatal infections: 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new/worsening signs or symptoms consistent with infection. For Grade 3/4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions Serious cutaneous reactions occurred. Grade 3: 4%, including photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new/worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for Grade 3 until resolution. Advise patients to: minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows; protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, consider dermatologic consultation.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to ADC Therapeutics at 1-855-690-0340.

AR = adverse reaction; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = overall response rate; NE = not estimable; PR = partial response; r/r = relapsed or refractory
Challenge expectations in 3L DLBCL

Take the next step...

...on the path to response with the first and only single-agent, CD19-directed ADC\(^1,2\)

<table>
<thead>
<tr>
<th>48.3(%) ORR(^a)^†‡</th>
<th>1.3 Months</th>
<th>Single-Agent IV(^1,b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI: 39.9, 56.7)(^1)</td>
<td>median time to response (range: 1.1–8.1)(^1)</td>
<td>30-minute infusion</td>
</tr>
<tr>
<td>24.1% CR; 24.1% PR(^‡)</td>
<td></td>
<td>Once every 3 weeks</td>
</tr>
<tr>
<td>(95% CI for each: 17.4, 31.9)(^1)</td>
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</tbody>
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\(^a\) Median duration of response: 10.3 months (95\% CI: 6.9, NE). Of 70 patients with objective response, 25 (36\%) were censored prior to 3 months; 26\% of responders had a DOR of ≥6 months.\(^1\)

\(^b\) Premedication: dexamethasone 4 mg (oral or IV) twice daily for 3 days, beginning the day before infusion. If dexamethasone administration does not begin the day before ZYNLONTA, it should begin at least 2 hours prior to ZYNLONTA infusion (unless contraindicated).\(^1\)

\(^‡\) Median follow-up time: 7.3 months (range: 0.3–20.2).\(^1\)

\(^\dagger\) ORR: n=70. CR: n=35. PR: n=35.\(^1\)

Embryo-Fetal Toxicity ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.

Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

ADVERSE REACTIONS In a pooled safety population (215 patients, Phase 1 and LOTIS-2), the most common (>20\%) ARs, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltranspeptidase (GGT), neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

In LOTIS-2, serious ARs occurred in 28\% of patients. The most common (>2\%) were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal ARs: 1\%, due to infection.

Please see Brief Summary of the full Prescribing Information on adjacent pages.

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**ADVERSE REACTIONS**
- Infections: occurred in 28\% of patients. The most common (>2\%) were pneumonia, urinary tract infection, and sepsis.
- Myelosuppression: occurred in 7\% of patients. The most common (>2\%) were neutropenia, thrombocytopenia, and anemia.
- Neutropenia: 32\%; thrombocytopenia: 20\%; anemia: 16\%.
- Grade 3/4 myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 15\%; thrombocytopenia: 15\%; anemia: 13\%.

**PRECAUTIONS**
- Pregnancy: ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells. Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 6 months after the last dose.

**DOSE DELAYS AND MODIFICATIONS**
- Permanent treatment discontinuation due to an AR of ZYNLONTA: 19\%. Of these, ≥2\% were increased GGT, edema, and effusion.
- Dose reductions due to an AR of ZYNLONTA: 8\%. Of these, ≥4\% was increased GGT.
- Dosage interruptions due to an AR of ZYNLONTA: 49\%. Of these, ≥5\% were increased GGT, neutropenia, thrombocytopenia, and edema.

For Grade ≥3 nonhematologic toxicity, hold ZYNLONTA until toxicity ≤Grade 1. For neutropenia: if ANC <1 x 10^9/L, hold ZYNLONTA until ANC ≥1 x 10^9/L. For thrombocytopenia: if platelet count <50,000/mcL, hold ZYNLONTA until ≥50,000/mcL. For Grade ≥2 edema or effusion, hold ZYNLONTA until ≤Grade 1. If dosing is delayed >3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation. Note: If toxicity requires dose reduction following second dose of 0.15 mg/kg (C2D1), patient should receive 0.075 mg/kg for Cycle 3.

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Zynlonta® loncastuximab tesirine-lypl
for injection, for intravenous use • 10mg
ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use

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

INDICATIONS AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Effusion and Edema. Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 4 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1%. Monitor patients for new or worsening edema or effusions. Hold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions.

Myelosuppression. Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytophenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony stimulating factor administration as applicable.

Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

Cutaneous Reactions. Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema. Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Embryo-Fetal Toxicity. Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic conjugate (SG3199) and affects actively dividing cells. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 9 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA, and for 6 months after the last dose (see Use in Specific Populations (8.1, 8.3)).

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

Effusion and Edema

Myelosuppression

Infections

Cutaneous Reactions

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles.

In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies (see Clinical Studies (14.1)). The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mU/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 3 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, edema, pericardial effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥2% was gamma-glutamyltransferase increased.

Dose interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2</th>
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<tbody>
<tr>
<td>Adverse Reaction</td>
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<tr>
<td>ZYNLONTA (N=145)</td>
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<tr>
<td>All Grades (%)</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
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<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Edema&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
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<tr>
<td>Rash&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Pruritus</td>
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<td>Photosensitivity reaction</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Abdominal pain&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vomiting</td>
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<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
</tr>
<tr>
<td>Musculoskeletal pain&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
</tr>
<tr>
<td>Decreased appetite</td>
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<td>Respiratory Disorders</td>
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<td>Dyspnea&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pleural effusion</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Upper respiratory tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup> Indicate treatment-emergent grade 3 or 4 adverse reactions occurring in >10% of patients.

<sup>*</sup> Indicate treatment-emergent adverse reactions occurring in ≥2% of patients.
Since its inaugural year in 2013, the OncLive® Giants of Cancer Care® program has celebrated the achievements of 126 leaders in the oncology and hematology field whose work has contributed to remarkable improvements in outcomes for countless patients with cancer. An advisory panel of eminent oncologists chooses the winners of these awards from an international roster of nominees. As the program marks its 10th season, Oncologylive® is featuring selected profiles of the pioneers and innovators whom we have been privileged to honor over the years. In this article, Joyce A. O’Shaughnessy, MD, describes how her patients have fostered a life long commitment to improving cancer care.

Joyce A. O’Shaughnessy, MD, may be an accomplished clinical investigator, researcher, and educator, but ultimately her patients drive her passion. “Every week, I am inspired by my patients; I wouldn’t be able to do it otherwise,” O’Shaughnessy said in an interview at the time of her Giants of Cancer Care® award reception. “The clinical care and the patients motivate me. [That] has kept me right where I am, and it is what gets me out of bed every morning.”

Her commitments in the clinic also fuel her desire to share knowledge with others, said O’Shaughnessy, who was named the 2016 Giant of Cancer Care® for Community Outreach/Education. She has served as a leader at numerous conferences and meetings, including as program chair for the International Congress on the Future of Breast Cancer®. She also helped to establish the School of Breast Oncology®, a meeting hosted by Physicians’ Education Resource®, LLC (PER®). She will continue to serve as the program director as the meeting enters its 21st year.

“I find my peers and colleagues turning to me, and I turn to them for help and guidance. It is usually about patient [treatment]; the goal is really about trying to help the individual patient,” said O’Shaughnessy, who is the Celebrating Women Chair in Breast Cancer Research at Baylor University Medical Center, Texas Oncology, and chair of the Breast Cancer Program at US Oncology Research. “I see the impact that education can have as I talk to [individuals who] have an experience that I haven’t had and, in turn, help teach and give suggestions to other doctors dealing with challenges that I have had.”

WHAT INSPIRED HER PASSION
The first patient to motivate O’Shaughnessy was her sister, Teri, who received a diagnosis of acute lymphoblastic leukemia at age 5 in 1970, when O’Shaughnessy was in high school. She was treated in clinical trials and for a time did well. O’Shaughnessy wanted to better understand the disease her sister was fighting and soon became interested in the biology of leukemia.

When Teri died in 1975, O’Shaughnessy had just started attending College of the Holy...
Cross in Worcester, Massachusetts. Her sister's death intensified her interest in fighting cancer, and although she was only a freshman biology student, O'Shaughnessy started conducting leukemia research with the Worcester Foundation for Experimental Biology (now called the Worcester Foundation for Biomedical Research).

"It was a bit unusual, but I made it a priority," said O'Shaughnessy. "It was very important to me. It was my No. 1 priority to get into cancer research immediately, and I wasn't going to wait until graduate school."

In 1978, O'Shaughnessy completed her undergraduate degree and continued studying leukemia at Yale School of Medicine in New Haven, Connecticut. After graduating in 1982 and completing her internship and residency at Massachusetts General Hospital in Boston in 1985, O'Shaughnessy did her oncology fellowship at the National Cancer Institute (NCI). There, in 1990, she made the switch from leukemia to breast cancer, where her focus remains today. She remained with the NCI until 1995 and then briefly worked at what is now the CBC Group at Loyola Medicine, who worked with her on capecitabine and gemcitabine, respectively.

Loyola Medicine, who worked with her on capecitabine and gemcitabine, respectively.

Despite her success, O'Shaughnessy is quick to acknowledge the support she received from mentors throughout her career. "It is always teamwork," O'Shaughnessy said. "The only way you can problem solve is with the right diagnostic and therapeutic tools. For some cancer situations, we do have the tools [but] we cannot problem solve. The only way to develop those tools is by clinical trials. You've got to come up with new strategies, new diagnostics, and new therapeutics."

However, O'Shaughnessy sees herself as a physician first and still credits her patients, especially those not responding to available treatments, as her primary motivation. It can be difficult to see patients and not be able to find a treatment that works for them, said O'Shaughnessy. "It is immensely frustrating to be calling on us to solve that problem," she said. "The only way you can problem solve is with the right diagnostic and therapeutic tools. For some cancer situations, we do have the tools [but] we cannot problem solve. The only way to develop those tools is by clinical trials. You've got to come up with new strategies, new diagnostics, and new therapeutics."

O'Shaughnessy looks forward to integrating new targeted therapies into the chemotherapy agent eribulin mesylate; the immune checkpoint inhibitor pembrolizumab (Keytruda); and numerous targeted therapies including HER2 and PARP inhibitors.

Over the past 3 years, the breast cancer landscape has seen a surge of approvals and O'Shaughnessy looks forward to integrating these advancements into clinical practice. "It's truly an exciting and hopeful time in breast cancer because many of the novel agents recently approved and in late-stage development will ultimately improve the long-term outcomes of patients with high-risk early-stage breast cancer—and there's no indication that the pace of discovery will slow down any time soon," she said in a recent interview with OncologyLive®.

FOCUSING ON THE FUTURE

Although she has accomplished so much in her career, O'Shaughnessy doesn't show any signs of slowing. She does, however, make time for friends and family.

Her current research is focused on trying to understand the molecular subtyping of triple-negative breast cancer (TNBC). Her goal is to understand the molecular biology of the subtypes and develop clinical trials to test the hypothesis on how to treat patients for whom there are no curative tools. This requires understanding how deficits in DNA repair in TNBC can be exploited to enhance the efficacy of novel agents such as immunotherapies.

Clinical trials also continue to be important to O'Shaughnessy. "As oncologists, patients are coming to us with a big problem and they are calling on us to solve that problem," she said. "The only way you can problem solve is with the right diagnostic and therapeutic tools. For some cancer situations, we do have the tools [but] we cannot problem solve. The only way to develop those tools is by clinical trials. You've got to come up with new strategies, new diagnostics, and new therapeutics."

O'Shaughnessy sees herself as a physician first and still credits her patients, especially those not responding to available treatments, as her primary motivation. It can be difficult to see patients and not be able to find a treatment that works for them, said O'Shaughnessy. "It is immensely frustrating to be asked to problem solve for a patient and not have the tools."
Efforts to Target NRG1 Unlock New Pathways for Treatment

by BRITTANY LOVELY

THE ADVENT AND IMPLEMENTATION

of advanced sequencing technologies in clinical practice have aided in the identification of highly active oncogenic gene fusions. RNA sequencing has illuminated the presence of NRG1 fusions, which, though rare, play a role in the activation of the ERBB pathway. Early data have demonstrated poor outcomes for patients with NRG1 fusions, and limited efficacy with available treatments represents a need for the development of novel therapeutic agents.

NRG1 fusions have been identified in several solid tumor types, including in patients with gallbladder, pancreatic, ovarian, breast, lung, bladder, and colorectal cancers, as well as sarcomas.¹

“[NRG1 fusions are seen] across a variety of solid tumors, but overall, the frequency is anywhere between 0.2% and 0.4%,” Janakiraman Subramanian, MD, MPH, said in a recent “Molecular Targets on the Horizon in Non–Small Cell Lung Cancer” OncLive® Scientific Interchange & Workshop panel discussion. “We’ve known about NRG1 fusions for years. They were initially detected in a lung adenocarcinoma by RNA sequencing, and the upstream partner for NRG1 that was originally detected was CD74; it’s a rare fusion in lung cancer.” Subramanian is director of thoracic oncology at Saint Luke’s Cancer Institute and an assistant professor of medicine at the University of Missouri-Kansas City.

UNCOVERING THE POPULATION WITH NRG1 FUSIONS

The NRG1 gene represents a unique cancer driver, encoding the neuregulin 1 protein, which functions as a ligand for HER3 and HER4 (FIGURE 3). Although the fusion is rare among patients with lung adenocarcinomas, with an overall frequency of approximately 1.7%, Subramanian noted that a higher prevalence, ranging from approximately 27% to 31%, occurs in patients with invasive mucinous adenocarcinomas, particularly those with wild-type KRAS disease.¹

A growing body of evidence supports the development of novel therapeutic strategies for patients with NRG1 fusions. “The clinical characteristics and response to traditional treatments have been essentially based on case reports until very recently, when we have [had] more updated data from the NRG1 registry,” Subramanian said.

According to an analysis of data from the eNRGy1 Global Multicenter Registry, investigators concluded that NRG1 fusion-positive lung cancers were “molecularly, pathologically, and clinically more heterogeneous than previously recognized” and “the activity of cytotoxic, immune, and targeted therapies was disappointing” among patients with rearranged tumor biology.⁵

In the data, investigators conducted an analysis of the activity of systemic therapy for patients with confirmed NRG1 fusion–positive lung cancer who were treated with platinum doublet–based chemotherapy (n = 15), taxane-based chemotherapy/immuno-therapy (n = 7), combination chemotherapy/immuno-therapy (n = 9), single-agent immunotherapy (n = 5), and targeted therapy with afatinib (Gilotrif; n = 20).³ The median progression-free survival (PFS) was 5.8 months (95% CI, 2.2-9.8), 4.0 months (95% CI, 0.8-5.3), 3.3 months (95% CI, 1.4-6.3), 3.6 months (95% CI, 0.9-undefined), and 2.8 months (95% CI, 1.9-4.3), respectively.

In terms of best response, 25% (5 of 20) of patients who received afatinib had a partial response compared with 13% (n = 2 of 15) of those who received platinum doublet-based chemotherapy, 14% (n = 1 of 7) of those who received taxane-based chemotherapy, and 20% (n = 1 of 5) of those who received single-agent immunotherapy. No complete or partial responses were recorded among the 9 patients who received combination chemotherapy/immuno-therapy; however 44% had stable disease.⁶

“As we can see, [results are] very depressing in terms of traditional treatments, [whether] platinum-based chemotherapy, second-line taxane, or a combination of chemoinmunotherapy,” Subramanian said. “Even where the response rates look relatively good, the median PFS and the CIs [and] the overall duration of benefit do not appear to be great for this population.”

BUILDING A FUTURE FOR NRG1

Subramanian highlighted an important finding from the study—the prevalence of NRG1 fusions outside patients with mucinous adenocarcinomas. “There were several patients with squamous cell carcinomas of the lung as well as large cell histology [who had] an NRG1 fusion, the bottom line being that we should be testing all these patients and not necessarily focusing on an enriched population.”

One such effort to develop a novel treatment for this patient population is the phase 2 CRESTONE trial (NCT04383210). Investigators are evaluating the efficacy of a novel HER3-targeted monoclonal antibody, seribantumab, in patients with advanced solid tumors with NRG1 fusions who have progressed after 1 or more prior lines of therapy.⁷

“HER3 is a truncated protein,” Subramanian said. “It does not have its own kinase, but it heterodimerizes with HER2 after it is activated by NRG1, [leading] to downstream pathway activation through PI3K/AKT pathway.” In preclinical models, seribantumab, a fully human IgG2 monoclonal antibody against HER3, has demonstrated the ability to block HER3-HER2 dimerization and downstream signaling, as well as block the ligand-dependent activation and phosphorylation of HER3.⁸

In CRESTONE, patients with NRG1 fusion–positive tumors—as determined by local clinical laboratory improvement amendments or a similarly accredited lab—who have received no prior treatment with pan-ERBB–HER2, or HER3-targeted therapy and who have no other actionable molecular alterations are eligible for enrollment. Eligible patients will receive 3 g of seribantumab intravenously over 1 hour weekly. The primary outcome in the intention-to-treat population is objective response rate per RECIST 1.1 criteria by independent central radiologic review. Secondary end points include duration of response, safety, PFS, overall survival, and clinical benefit rate.

INTEGRATING TESTING INTO PRACTICE IS A TOP PRIORITY

Outside clinical trials, Paul A. Bunn Jr, MD, who served as moderator for the OncLive® program, noted that actionable treatments will rely on the identification of these fusions through testing in clinical practice. Bunn is a 2014 Giants of Cancer Care® award winner in the lung cancer category, the James Dudley Chair in Cancer Research, and distinguished professor of medicine–medical oncology at the University of Colorado School of Medicine in Aurora.

Bunn cited data from the 2021 American Society of Clinical Oncology Meeting that showed that rates of testing for mutations in
community practice are low. Specifically, results showed that among 3,474 adults with non-small cell lung cancer (NSCLC), 90% underwent testing for 1 biomarker, but less than half (46%) received testing for 5 actionable mutations, including ALK, BRAF, EGFR, ROS1, and PD-L1. He posed the question: “Because NRG1 is detected by RNA sequencing, what do you think should be the standard testing? Do you believe everybody should have RNA and DNA testing, or should people have selective testing?”

Subramanian said that as investigators continue to evaluate the efficacy of novel NRG1-targeted agents, awareness will play a large role in the community setting in terms of integrating testing as standard practice. “My personal opinion is that we should be testing everybody, and we should be using both DNA and RNA,” he said. “[Data from] the NRG1 registry show that in approximately 75% of patients with NRG1 fusions, they were detected by an RNA sequencing platform; approximately 25% DNA-based deduction was reported.” He added that RNA sequencing-based deduction combined with DNA-based deduction appears to provide the highest likelihood of detecting NRG1 fusions.

Subramanian concluded that testing is particularly important among patients with NSCLC. “We can see that NRG1 fusions are not necessarily specific to 1 subtype of NSCLC. It’s a little bit more diverse across the histologic subtypes, and we see that standard-of-care treatments for these patients—chemotherapy, immunotherapy, or even afatinib—do not hold a lot of promise. Identifying this fusion and, hopefully, having available either a [tyrosine kinase inhibitor] or a monoclonal antibody might be the best option for these patients.”

Room for optimism exists in the community setting, said Subramanian, who added, “We interact with a lot of colleagues in the community, and there is awareness that molecular testing is important. The problem is for a busy community oncologist who is seeing 20 to 30 patients—they are not chasing after testing. Promoting testing and making sure it gets incorporated with an [electronic medical record] would be key [to ensure] ordering and testing can be done far more easily for these busy clinicians.”

REFERENCES
Median time to first onset was 2.8 months (range: 1.2 to 21.0).

Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

**Important Safety Information**

**Indication**
ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

**Contraindications**
None.

**Warnings and Precautions**

**Interstitial Lung Disease / Pneumonitis**
Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with ENHERTU. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, ILD occurred in 10% of patients. Median time to first onset was 2.8 months (range: 1.2 to 21.0).

**WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY**
-Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms.
-Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception.

**Please see Important Safety Information continued on the next page, and Brief Summary of Prescribing Information, including Boxed WARNINGS on the following pages.**
Important Safety Information (cont.)

Adverse reactions to ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF. Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF <50% prior to initiation of treatment. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. When LVEF is <45% and absolute decrease from baseline is 10-20%, continue treatment with ENHERTU. When LVEF is 40-45% and absolute decrease from baseline is <10%, continue treatment with ENHERTU and repeat LVEF assessment within 3 weeks. When LVEF is 40-45% and absolute decrease from baseline is 10-20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, permanently discontinue ENHERTU. If LVEF recovers to within 10% from baseline, resume treatment with ENHERTU at the same dose. When LVEF is <40% or absolute decrease from baseline is >20%, interrupt ENHERTU and repeat LVEF assessment within 3 weeks. If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue ENHERTU. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure.

Embryo-Fetal Toxicity
ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose of ENHERTU.

Additional Dose Modifications
Thrombocytopenia
For Grade 3 thrombocytopenia (platelets <50 to 25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less, then maintain dose. For Grade 4 thrombocytopenia (platelets <25 x 10^9/L) interrupt ENHERTU until resolved to Grade 1 or less. Reduce dose by one level.

Adverse Reactions
The safety of ENHERTU was evaluated in 187 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in DESTINY-Gastric01. Patients intravenously received at least one dose of either ENHERTU (N=125) 6.4 mg/kg once every three weeks or either irinotecan (N=62) 150 mg/m^2 biweekly or paclitaxel (N=7) 80 mg/m^2 weekly for 3 weeks. The median duration of treatment was 4.6 months (range: 0.7 to 22.3) in the ENHERTU group and 2.8 months (range: 0.5 to 13.1) in the irinotecan/paclitaxel group. Serious adverse reactions occurred in 44% of patients receiving ENHERTU 6.4 mg/kg. Serious adverse reactions in >2% of patients who received ENHERTU were decreased appetite, ILD, anemia, dehydration, pneumonia, cholestatic jaundice, pyrexia, and tumor hemorrhage. Fatalities due to adverse reactions occurred in 2.4% of patients: disseminated intravascular coagulation, large intestine perforation, and pneumonia occurred in one patient each (0.8%). ENHERTU was permanently discontinued in 15% of patients, of which ILD accounted for 5%. Dose interruptions due to adverse reactions occurred in 62% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose interruption were neutropenia, anemia, decreased appetite, leukopenia, fatigue, thrombocytopenia, ILD, pneumonia, cholestasis, upper respiratory tract infection, diaphoresis, and hypokalemia. Dose reductions occurred in 32% of patients treated with ENHERTU. The most frequent adverse reactions (>2%) associated with dose reduction were neutropenia, decreased appetite, fatigue, nausea, and febrile neutropenia.

The most common (>20%) adverse reactions, including laboratory abnormalities, were hemoglobin decrease (75%), white blood cell count decrease (74%), neutrophil count decrease (72%), lymphocyte count decrease (70%), platelet count decrease (68%), neumonia (63%), decreased appetite (62%), anemia (58%), aspartate aminotransferase increased (58%), fatigue (55%), blood alkaline phosphatase increased (54%), alanine aminotransferase increased (47%), diaphoresis (32%), hypokalemia (30%), vomiting (26%), constipation (24%), blood bilirubin increased (24%), pyrexia (24%), and alopecia (22%).

Use in Specific Populations
• Pregnancy: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risks to a fetus. There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU.
• Lactation: There are no data regarding the presence of ENHERTU in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.
• Females and Males of Reproductive Potential: Pregnancy testing: Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU. Contraception: Females: ENHERTU can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose. Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months following the last dose. Infertility: ENHERTU may impair male reproductive function and fertility.
• Pediatric Use: Safety and effectiveness of ENHERTU have not been established in pediatric patients.
• Geriatric Use: Of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg in DESTINY-Gastric01, 56% were ≥65 years and 14% were ≥75 years. No overall differences in efficacy or safety were observed between patients ≥65 years of age compared to younger patients.
• Hepatic Impairment: In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or fda.gov/medwatch. Please see Brief Summary of Prescribing Information on the next pages.
ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use

5.1 Metastatic Breast Cancer
ENHERTU is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

This indication is approved under accelerated approval based on tumor response rate and duration of response [see Clinical Studies (14.1) in the full prescribing information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

5.2 Neutropenia
Severe neutropenia, including febrile neutropenia, can occur in patients treated with ENHERTU [see Adverse Reactions (6.1)]. Advise patients to immediately report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms. Monitor patients for signs and symptoms of ILD. Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist. For asymptomatic (Grade 1) ILD, consider corticosteroid treatment (e.g., 20-30 mg/day prednisolone or equivalent). Withhold ENHERTU until recovery [see Dosage and Administration (2.3) in the full prescribing information]. In cases of symptomatic ILD (Grade 2 or greater), promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisolone or equivalent) and continue for at least 14 days followed by taper for at least 4 weeks. Permanently discontinue ENHERTU in patients who are diagnosed with symptomatic (Grade 2 or greater) ILD [see Dosage and Administration (2.3) in the full prescribing information].

5.3 Left Ventricular Dysfunction
Patients treated with ENHERTU may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including ENHERTU. In the 234 patients with unresectable or metastatic HER2-positive breast cancer who received ENHERTU, two cases (0.9%) of asymptomatic LVEF decrease were reported. In DESTINY-Gastric01, of the 125 patients with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with ENHERTU 6.4 mg/kg, no clinical adverse events of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in LVEF.

Treatment with ENHERTU has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment. Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage LVEF decrease through treatment interruption. Permanently discontinue ENHERTU if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF) [see Dosage and Administration (2.3) in the full prescribing information].

5.4 Embryo-Fetal Toxicity
Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. In postmarketing reports, exposure of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, oxaliplatin, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells [see Use in Specific Populations (8.1)].

Verify the pregnancy status of females of reproductive potential prior to the initiation of ENHERTU. Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of ENHERTU. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU.

6. ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:

• Intestinal Lymph Disease/Pneumonitis [see Warnings and Precautions (5.1)]
• Neutropenia [see Warnings and Precautions (5.2)]
• Left Ventricular Dysfunction [see Warnings and Precautions (5.3)]

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

Metastatic Breast Cancer
The safety of ENHERTU was evaluated in a pooled analysis of 234 patients with unresectable or metastatic HER2-positive breast cancer who received at least one dose of ENHERTU 5.4 mg/kg in DESTINY-Breast01 and Study DS8201-A-J101 (NCT02564900) [see Clinical Studies (14.1) in the full prescribing information]. ENHERTU was administered by intravenous infusion once every three weeks. The median duration of treatment was 7 months (range: 0.7 to 31). In the pooled 234 patients, the median age was 56 years (range: 28-96); 74% of patients were ≥65 years, 89.6% of patients were female, and the majority were White (51%) or Asian (42%). Patients had an ECOG performance status of 0 (38%) or 1 (42%) at baseline. Ninety-four percent had visceral disease, 31% had bone metastases, and 13% had brain metastases.

Serious adverse reactions occurred in 20% of patients receiving ENHERTU. Serious adverse reactions in ≥1% of patients who received ENHERTU were interstitial lung disease, pneumonia, vomiting, nausea, cellulitis, hypokalemia, and intestinal obstruction. Fatalities due to adverse reactions occurred in 4.3% of patients including interstitial lung disease (2.6%), and the following events occurred in one patient each (0.4%): acute hepatic failure/acute kidney injury, general physical health deterioration, pneumonia, and hemorrhagic shock.

ENHERTU was permanently discontinued in 9% of patients, of which 6% accounted for Dose interruptions due to adverse reactions. In 33% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose interruption were neutropenia, anemia, thrombocytopenia, ILD, pneumonia, respiratory tract infection, fatigue, nausea, and ILD. Dose reductions occurred in 18% of patients treated with ENHERTU. The most frequent adverse reactions (≥2%) associated with dose reduction were fatigue, nausea, and neutropenia.

The most common (≥20%) adverse reactions, including laboratory abnormalities, were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough.
Tables 3 and 4 summarize common adverse reactions and laboratory abnormalities observed in ENHERTU-treated patients.

### Table 3: Common Adverse Reactions (≥10% All Grades or ≥2% Grades 3 or 4) in Patients in DESTINY-Breast01 and Study DS8201-A-J101

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
<th>All Grades %</th>
<th>Grades 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>79</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>47</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>35</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>59</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>46</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td>2.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and Infestation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry eye</td>
<td>11</td>
<td>0.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term. Percentages were calculated using the number of patients in the Safety Analysis Set as the denominator.

<sup>a</sup> Grouped term of abdominal pain includes PTs of abdominal discomfort, gastrointestinal pain, abdominal pain, abdominal pain lower, and abdominal pain upper.

<sup>b</sup> Grouped term of stomatitis includes PTs of stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, and oral mucosa blistering. One Grade 1 event of aphthous ulcer was not included in the summary of grouped term stomatitis (from DESTINY-Breast01).

<sup>c</sup> Grouped term of fatigue includes PTs of fatigue and asthenia.

<sup>d</sup> This Grade 3 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for alopecia is Grade 3.

<sup>e</sup> Grouped term of rash includes PTs of rash, rash pustular, and rash maculo-papular.

<sup>f</sup> Grouped term of anemia includes PTs of anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased.

<sup>g</sup> Intestinal lung disease includes events that were adjudicated as ILD: pneumonitis, interstitial lung disease, respiratory failure, organizing pneumonia, acute respiratory failure, lung infiltration, lymphangitis, and alveolitis.

<sup>h</sup> All events had total outcomes (n=6).

<sup>i</sup> Grouped term of headache includes PTs of headache, sinus headache, and migraine.

<sup>j</sup> Grouped term of upper respiratory tract infection includes PTs of influenza, influenza-like illness, and upper respiratory tract infection.

<sup>k</sup> This Grade 4 event was reported by the investigator. Per NCI CTCAE v.4.03, the highest NCI CTCAE grade for dry eye is Grade 3.

Other clinically relevant adverse reactions reported in less than 10% of patients were:

- Injury, Poisoning and Procedural Complications: infusion-related reactions (2.8%)
- Blood and Lymphatic System Disorders: febrile neutropenia (1.7%)

### Table 4: Selected Laboratory Abnormalities in Patients with Unresectable or Metastatic HER2-positive Breast Cancer Treated with ENHERTU

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU 5.4 mg/kg N=234</th>
<th>All Grades %</th>
<th>Grades 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>70</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>70</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>62</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>41</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>38</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>26</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Percentages were calculated using patients with worsening laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator.

Frequencies were based on NCI CTCAE v.4.03 grade-derived laboratory abnormalities.

### Table 5: Adverse Reactions in ≥10% All Grades or ≥2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU 5.4 mg/kg N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
<th>All Grades %</th>
<th>Grades 3 or 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>63</td>
<td>4.8</td>
<td>47</td>
<td>1.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>2.4</td>
<td>32</td>
<td>1.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>24</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>0.8</td>
<td>15</td>
<td>3.2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>11</td>
<td>1.6</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>80</td>
<td>17</td>
<td>45</td>
<td>13</td>
</tr>
<tr>
<td>Dehydration</td>
<td>7</td>
<td>2.4</td>
<td>3.2</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>58</td>
<td>38</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4.8</td>
<td>4.8</td>
<td>3.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

(continued)
Events were graded using NCI CTCAE version 4.03. N = number of patients exposed; PT = preferred term.

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- Cardiac Disorders: asymptomatic left ventricular ejection fraction decrease (6%)
- Infections and Infestations: pneumonia (6%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (1.6%)

Other clinically relevant adverse reactions reported in less than 10% of patients were:
- Cardiac Disorders: asymptomatic left ventricular ejection fraction decrease (6%)
- Infections and Infestations: pneumonia (6%)
- Injury, Poisoning and Procedural Complications: infusion-related reactions (1.6%)

Table 5: Adverse Reactions in ≥10% All Grades or >2% Grades 3 or 4 of Patients Receiving ENHERTU in DESTINY-Gastric01

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENHERTU N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>8</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Adverse Reactions All Grades %  Grades 3 or 4 %  All Grades %  Grades 3 or 4 %

Hematology

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ENHERTU N=125</th>
<th>Irinotecan or Paclitaxel N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3 or 4 %</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>74</td>
<td>29</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>47</td>
<td>9</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30</td>
<td>4.8</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

Percentages were calculated using patients with nonmissing laboratory values from baseline and the number of patients with both baseline and post-treatment measurements as the denominator. Frequencies were based on NCI CTCAE v 4.03 grade-derived laboratory abnormalities.

6.2 Immunogenicity

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

Treatment-induced anti-fam-trastuzumab deruxtecan-nxki antibodies (ADA) developed in 1.7% (14/807) patients who received ENHERTU across all doses. Due to the limited number of patients who tested positive for ADA, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy or safety. In addition, neutralizing activity of anti-ENHERTU antibodies has not been assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ENHERTU can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see Data). Based on its mechanism of action, the topoisomerase inhibitor component of ENHERTU, DXd, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells (see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information). Advise patients of the potential risks to a fetus.

There are clinical considerations if ENHERTU is used in pregnant women, or if a patient becomes pregnant within 7 months following the last dose of ENHERTU (see Clinical Considerations).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ENHERTU during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

There are no available data on the use of ENHERTU in pregnant women. In postmarketing reports in pregnant women receiving a HER2-directed antibody, cases of oligohydramnios manifesting as fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported. These case reports described oligohydramnios in pregnant women who received a HER2-directed antibody either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after use of a HER2-directed antibody was stopped.

Animal Data

There were no animal reproductive or developmental toxicity studies conducted with fam-trastuzumab deruxtecan-nxki.

8.2 Lactation

Risk Summary

There is no data regarding the presence of fam-trastuzumab deruxtecan-nxki in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ENHERTU and for 7 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of ENHERTU.

Contraception

Female

ENHERTU can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)). Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months following the last dose (see Nonclinical Toxicology (13.1) in the full prescribing information).

Infertility

Based on findings in animal toxicity studies, ENHERTU may impair male reproductive function and fertility (see Nonclinical Toxicology (13.1) in the full prescribing information).

8.4 Pediatric Use

Safety and effectiveness of ENHERTU have not been established in pediatric patients.

8.5 Geriatric Use

Of the 234 patients with HER2-positive breast cancer treated with ENHERTU 5.4 mg/kg, 26% were 65 years or older and 5% were 75 years or older. No overall differences in efficacy were observed between patients 65 years of age compared to younger
8.6 Renal Impairment
No dose adjustment of ENHERTU is required in patients with mild (creatinine clearance [CrCl] <60 and >90 mL/min) or moderate (CrCl ≥30 and <60 mL/min) renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No data are available in patients with severe renal impairment.

8.7 Hepatic Impairment
No dose adjustment of ENHERTU is required in patients with mild (total bilirubin <ULN and any AST >ULN or total bilirubin ≥1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor, DXd [see Dosage and Administration (2.3) in the full prescribing information]. No data are available in patients with severe (total bilirubin ≥3 to 10 times ULN and any AST) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

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

Interstitial Lung Disease
• Inform patients of the risks of severe or fatal ILD. Advise patients to contact their healthcare provider immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms [see Warnings and Precautions (5.1)].

Neutropenia
• Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection [see Warnings and Precautions (5.2)].

Left Ventricular Dysfunction
• Advise patients to contact their healthcare provider immediately for any of the following: new onset or worsening shortness of breath, cough, fatigue, swelling of ankles/legs, palpitations, sudden weight gain, dizziness, loss of consciousness [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity
• Inform female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.4), Use in Specific Populations (8.1)].
• Advise females of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 7 months after the last dose [see Use in Specific Populations (8.3)].
• Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ENHERTU and for at least 4 months after the last dose [see Use in Specific Populations (8.3)].

Lactation
• Advise women not to breastfeed during treatment and for 7 months after the last dose of ENHERTU [see Use in Specific Populations (8.2)].

Infertility
• Advise males of reproductive potential that ENHERTU may impair fertility [see Use in Specific Populations (8.2)].
Key Data Illuminate New Directions in HER2-Positive Metastatic Breast Cancer Landscape

by BRITTANY LOVELY

AN ABUNDANCE OF RICHES in the form of new data for HER2-targeted agents continues to drive progress for patients with metastatic breast cancer. Efforts to address disease have resulted in the repurposing and movement of established agents in lines of therapy, the designing of basket and adaptive trials used to explore therapeutic avenues, and the development of novel agents to fill clinical gaps for patients with limited options.

There was no shortage of data for patients with HER2-positive metastatic breast cancer at the 2021 San Antonio Breast Cancer Symposium (SABCS). Investigators arrived with updates from several key trials, including the following:

- DESTINY-Breast03 (NCT03529110): a phase 3 study evaluating fam-trastuzumab deruxtecan-nxki (Enhertu) vs ado-trastuzumab emtansine (T-DM1; Kadcyla) in patients with HER2-positive, unresectable and/or metastatic breast cancer, previously treated with trastuzumab (Herceptin) and a taxane; 1
- PHOEBE (NCT03080805): a phase 3 trial examining pyrotinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer; and 2
- SUMMIT (NCT01953926): a phase 2 basket study evaluating the efficacy of neratinib added to trastuzumab with or without fulvestrant among patients with triple-negative breast cancer (TNBC) and those with hormone receptor-positive, HER2-negative, HER2-mutant breast cancer. 3

As part of an OncLive® Breast Cancer Talk, Virginia G. Kaklamani, MD, moderated a discussion of the top takeaways from SABCS 2021 with a panel of breast cancer experts including Anne P. O’Dea, MD; Yara Abdou, MD; and Heather McArthur, MD.

In addition to discussing updated data from the landmark trials, the panel shared insights on 2 novel bispecific agents and how the landscape may be shifting toward leveraging these agents in the future. Data from 2 phase 1 trials were discussed:

- NCT03619681: evaluating KN026, a first-in-human HER2 bispecific antibody in combination with chemotherapy for patients with HER2-positive advanced breast cancer; 4
- NCT02892123: evaluating zanidatamab in combination with chemotherapy for patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab (Perjeta), and T-DM1. 5

Finally, the panel turned their attention to a read out from the I-SPY 2 Trial (NCT01042379), in which investigators explored the rationale of adding tucatinib to a taxane and dual HER2 blockade. 6 Results ranged from promising to null and void, leaving investigators with clear directions on which avenues are worth pursuing in future endeavors and which ones are proving to be dead ends.

[Prior to SABCS 2021], Sara Hurvitz, MD, presented [data from] key subgroups for DESTINY-Breast03 at the European Society for Medical Oncology [ESMO] Annual Congress 2021. She specifically talked about the patients who had clinically stable brain metastasis [at baseline]—15% of the overall trial population [n = 524]. 1 She reminded us that in some of the data presented at ESMO the objective response rate was much better, of course, for trastuzumab deruxtecan regardless of subgroup. Whether you look at estrogen receptor status, presence of visceral metastasis, or number of
lines of prior therapy, whatever subgroup you look at the objective response rate was much better with trastuzumab deruxtecan compared with T-DM1. The objective response rate was 79.7% [with trastuzumab deruxtecan (n = 261)] with a very impressive hazard ratio of 0.28.

What they then looked at in more detail and [presented at SABCS] was the key subgroup of patients with brain metastasis—and they gave us a lot of granularity on the data in terms of {for instance, the} intracranial [results (TABLE 1)]. If we look at the median progression-free survival [PFS] with trastuzumab deruxtecan, it was 15 months with 3 months with T-DM1 with a hazard ratio of 0.25. If we look specifically at intracranial responses, of the 72 patients with brain metastasis [who had target or nontarget lesions at baseline by imaging], the intracranial objective response rate was 63.9% with trastuzumab deruxtecan. Importantly, 28% of patients had complete responses ([CRs], which is), very exciting for these patients. This was compared with an intracranial response of 33.4% with T-DM1, with a CR rate for T-DM1 of 3%. We know that interstitial lung disease [ILD] is a potential toxicity with this compound, and in the earlier phases of [the DESTINY] studies we’ve seen some grade 5 [events in the data]. In DESTINY-Breast03, however, there were no cases of grade 5 ILD. In fact, there was no grade 4 ILD [either]. The overall rate of ILD was 10.5% [and] that was a very important safety signal.

**KAKLAMANI**  This was one of the most important trials presented this year, not just at SABCS, and I wanted to put [the data] into perspective. What are your thoughts about trastuzumab deruxtecan and where it sits in metastatic HER2-positive breast cancer?

**ABDOU**  [The data are] remarkable, … magnificent, and [have] definitely changed the treatment paradigm for patients with HER2-positive metastatic breast cancer. I would definitely [use] this drug in the second-line setting. Even though T-DM1 was our effective easy-to-give therapy, trastuzumab deruxtecan has remarkable data [and] is going to change the outcomes for these patients.

As Dr O’Dea alluded, the safety signal was quite reassuring. I think as part of that we’re a little more comfortable with identifying these adverse effects and maybe giving this drug in an earlier setting where patients are less vulnerable to developing pulmonary toxicity. That being said, [on account of] the lower ILD signal and the remarkable data that were presented, I would definitely change my treatment paradigm to use trastuzumab deruxtecan in the second-line setting.

**KAKLAMANI**  Dr McArthur, based on the results presented here and the pretty impressive response rate and PFS in patients with stable brain metastasis, how are you thinking about these patients in that second-line setting if you’re finding brain metastasis?

**MCARTHUR**  [Trastuzumab deruxtecan] has really become a standard of care in the second line and these are really exciting data in a subset of patients. Again, these are patients with clinically stable and treated brain metastasis, so a slightly different population than the patients with brain metastasis who participated in the HER2CLIMB study [NCT02614794].

One question that came up in the Q&A after the session was around the potential for radiation necrosis. There had to be at least 2 weeks between the end of whole brain radiation and study treatment, and those data are forthcoming. There will be some interest around CNS [central nervous system]-specific toxicity.

But it is particularly interesting to me because an antibody-drug conjugate we think of as being such a large molecule and the blood-brain barrier as being impenetrable to these large molecules. It challenges our thinking [on] how, historically, we’ve thought about how drugs get into the CNS—whether there are transportation mechanisms that we don’t understand [or] whether it’s systemic release of the drug that somehow penetrates the CNS has yet to be determined. But overall, [these are] really exciting data.

**KAKLAMANI**  Let’s move on to our second abstract, which [concerns] updated overall survival results from the phase 3 PHOEBE trial, pyrotinib vs lapatinib in combination with capecitabine in patients with HER2-positive metastatic breast cancer. Dr Abdou, would you like to help us understand the trial?

**ABDOU**  Pyrotinib is a second-generation irreversible pan-HER tyrosine kinase inhibitor [TKI], targeting HER1, HER2, and HER4. PHOEBE [investigators] evaluated pyrotinib plus capecitabine vs lapatinib plus capecitabine among patients with previously treated HER2-positive metastatic breast cancer. In the interim analysis, [whose findings were] published in *Lancet Oncology*, the pyrotinib combination significantly improved PFS compared with lapatinib, but the overall survival data were still immature.

At SABCS, we [listened to findings from] the updated analysis of the overall survival from this trial at the data cut-off, which was approximately 33 months’ follow-up. Among 267 patients enrolled in the study, patients who were treated with pyrotinib plus capecitabine had a 31% lower risk of death than those treated with lapatinib plus capecitabine. The [median] overall survival was not reached in the pyrotinib arm compared with 26.9 [months] in the lapatinib arm, [and] the hazard ratio was 0.69. The subgroup analysis of overall survival and PFS confirmed the benefit of pyrotinib across most of the clinically relevant subgroups.

I do want to point out though that neither pertuzumab nor T-DM1 [had been] approved in China at the time of patient enrollment, and therefore the study was unable to assess the efficacy of the combination regimen in patients previously treated with either of those therapies, making it hard to extrapolate data to the US population. However, this is a reasonable second-line option in countries and regions where access to HER2-targeted therapies is scarce.

As you mentioned, T-DM1 [is] available in China but agents such as trastuzumab deruxtecan or tucatinib [are not available]. So for that patient population, pyrotinib would be a wonderful option.

Our third abstract, [focuses on data of] neratinib with fulvestrant and trastuzumab for hormone receptor-positive mutant metastatic breast cancer, and neratinib plus trastuzumab for triple-negative breast cancer. [These are...]

| TABLE. Response in CNS Subgroups of DESTINY-Breast03 Trial |
|-----------------------------|---------------|---------------|
| Outcome                  | Trastuzumab deruxtecan (n = 43) | T-DM1 (n = 39) |
| ORR                       | 67.7%          | 20.5%          |
| CR                        | 4.7%           | 0%             |
| PR                        | 62.8%          | 20.5%          |
| DCR                       | 93.0%          | 76.9%          |
| Median DOR, months (95% CI) | 12.9 (8.5-NE)  | 7.2 (2.8-NE)  |

**Intracranial response per BICR using RECIST 1.1**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab deruxtecan (n = 36)</th>
<th>T-DM1 (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with objective response, n</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>CR</td>
<td>27.8%</td>
<td>2.8%</td>
</tr>
<tr>
<td>PR</td>
<td>36.1%</td>
<td>30.6%</td>
</tr>
</tbody>
</table>
the latest updates from the SUMMIT trial [NCT01953926], another important trial we’re all looking forward to seeing data from. Dr McArthur, what are your thoughts about the trial?

**McArthur**

Komal Jhaveri, MD, from Memorial Sloan Kettering Cancer Center, gave a fantastic update from the SUMMIT trial. HER2 mutations in the absence of gene amplification or protein overexpression are a unique mechanism of oncogenic addiction to HER2 signaling. They’re rare, they occur only in approximately 2% to 12% of tumors, and [Jhaveri] gave a nice breakdown... actually of incidence in specific subsets of breast cancer—2% in primary breast tumors, 2% to 4% in metastatic breast cancer overall.

[The update from that study is a little bit complicated [FIGURE 3]. There are multiple different arms, including] a TNBC arm comprising 18 patients who were treated with the doublet, neratinib with trastuzumab. There was an overall response rate in those 18 patients of 33% with a median PFS of 6.2 months.

The rest of the study focused on the hormone receptor–positive, HER2-negative, HER2-mutant population. There was 1 nonrandomized arm that combined neratinib with fulvestrant and trastuzumab and that population had an overall response rate of 46%, which I thought was impressive, and a median PFS of 8.2 months. In a second part of that study, there was randomization of patients with hormone receptor–positive, HER2-negative, HER2-mutant [disease], and [this arm] was designed to tease out the contributions of each of the components of the triplet regimens.

Seven patients were randomized to receive the triplet, 7 patients received fulvestrant with trastuzumab, and another 7 patients received fulvestrant alone. What I thought was remarkable was that [patients in the] 2 arms of the 3-arm randomization who did not receive neratinib had a 0% overall response rate, whereas those in the triplet arm, again a small group, [had] an overall response rate of 29%

Combining both the nonrandomized arm and [those in the] randomized arm who received the triplet, the overall response rate with that triplet was 42%. The median PFS was 7 months and, interestingly, [these data were] after prior CDK exposure. It appears, based on the absence of response rate without neratinib, that neratinib [is] critical for inhibition of HER2-mutant breast cancer. [It is] worth noting that there is a cost in the form of toxicity—approximately 90% of patients experienced diarrhea of any grade and just over 80% of patients experienced nausea. Loperamide prophylaxis is critically important when these combinations are to be administered.

**O’dea**

Dr McArthur, did [investigators] use dose escalation for the neratinib in that trial or was it just loperamide prophylaxis?

**McArthur**

There was not a prophylactic regimen which is why the rate was so high at 90%.

**Kaklamani**

That’s a great point, Dr O’Dea. We know from the control trial that if we give neratinib at the dose escalation, patients do significantly better because the diarrhea is just so dreadful. The ER-positive group was impressive but I kept looking at the triple-negative group—no chemotherapy and a monoclonal antibody, trastuzumab, plus neratinib...
giving us a response rate of 33.3%. That’s pretty impressive as well, right?

**MCARTHUR**

It’s amazing. I mean, [these are] small numbers again, only 18 patients participating in that triple-negative cohort. But it is incredible that you could have…a nonchemotherapeutic regimen to treat triple-negative disease and that’s one more thing, potentially, [for] our arsenal.

**KAKLAMANI**

If next week you send a patient for molecular testing and they come back with a HER2 mutation, would you consider giving neratinib?

**MCARTHUR**

[If I had a patient] enrolled on the SUMMIT trial when I was [at Memorial Sloan Kettering] and she did exceptionally well after progressing very quickly on prior lines of therapy. So I have used neratinib in selected patients. Again, these mutations are relatively rare, but I have used [the drug] in selected patients with success. [However], as Dr Jhaveri said, it’s not ready for prime time based on these relatively small numbers.

**ABDOU**

It would be interesting to look at the molecular biology of these tumors, specifically in TNBC, to see if they have a specific heterogeneity depending on that mutation.

**KAKLAMANI**

Most mutations happen in the kinase part of HER2 as well, which is also important. [But] there did not seem to be much of a difference in response, depending on where those mutations were.

Our next abstract, [has data for] a first-in-human HER2-targeted bispecific antibody, KN026, for the treatment of patients with HER2-positive metastatic breast cancer, results from a phase 1 trial. Dr O’Dea, would you like to go over this poster with us?

**O’DEA**

This was looking at a novel bispecific antibody that binds to 2 distinct HER2 epitopes. It was given as monotherapy for HER2-positive metastatic breast cancer in a phase 1 dose escalation [trial] using a 3+3 dose escalation rule followed by a dose-expansion cohort. There were 63 patients [evaluated and the] recommended phase 2 dose was 20 mg every 2 weeks or 30 mg every 3 weeks. [At that] dose the overall response rate was 28.1% and the median PFS was 6.8 months among 57 patients.

Investigators completed a series of translational studies in 20 of the patients with confirmed coamplification of CDK12. They found that to be a promising biomarker. If you looked at the patients that had coexpression of CDK12, the overall response rate was 50% compared with 0% without the coexpression, so [that is] very encouraging. And if you looked at the median PFS in the group with the coexpression, it was 8.2 months vs lack of coexpression, [for which it was] 2.7 months. The authors’ conclusions were that KN026 was well tolerated overall [and it] achieved comparable efficacy [with the] trastuzumab and pertuzumab doublet even in a more heavily pretreated population. It appears that the coamplification of HER2 and CDK12 may predict who will derive benefit from this new compound.

**KAKLAMANI**

Some of the adverse reactions [included] fever, diarrhea, and some liver toxicity, [and] most of them were grade 1 and 2. That 50% [response rate] is impressive [for] an antibody.

The next abstract looks at [data from a phase 1 study] of another bispecific antibody, zanidatamab, or ZW25, in combination with chemotherapy for HER2-positive breast cancer. Dr Abdou, would you like to give us your thoughts on this trial?

**ABDOU**

Zanidatamab is a HER2-targeted bispecific antibody which is directed at 2 domains of the HER2 protein—EZD4 and EZD2—and simultaneously binds to 2 distinct sites on the HER2 resulting in increased antibody binding, receptor clustering, and then downregulation of the HER2 receptor. The data presented at SABCS are results from an ongoing phase 1 clinical trial [in which] 20 patients with heavily pretreated HER2-positive metastatic breast cancer were enrolled and had received zanidatamab in combination either with Navelbine, or capecitabine, or paclitaxel.

I would like to point out that 9 of these patients had stable brain metastasis at the time of enrollment, which was allowed on the trial, and patients [had] received a median of 3 prior HER2 regimens. In 16 of the patients evaluable for efficacy, treatment with zanidatamab and chemotherapy resulted in an objective response rate of 36.4% and a disease control rate of 86.4%. The median PFS was 7.3 months across all the treatment arms, and the median duration of response was not reached.

Among all patients [n = 20] zanidatamab with chemotherapy was pretty well tolerated. … A majority of adverse effects [were] considered mild to moderate and the most common…were diarrhea, nausea, and peripheral neuropathy, which I suspect…were [mostly] due to chemotherapy, not the anti-HER2 agent. These data definitely support further investigation of zanidatamab as a novel therapeutic agent for HER2-positive breast cancer, and my understanding is they’re also evaluating the combination with tucatinib, which will be interesting to see.

**KAKLAMANI**

Another impressive bispecific antibody. They’re becoming a little more common in our phase 1 trials, right? When I looked at these data, this disease control rate of 86.4% really caught my attention. In these heavily pretreated patients, that’s a good number to have.

Let’s move on to the poster discussion of tucatinib plus paclitaxel and pertuzumab-trastuzumab followed by AC in [patients with] high-risk HER2-positive breast cancer with stage II or III disease, [the] results from the I-SPY trial. Dr McArthur, what are your thoughts here?

**MCARTHUR**

As you know, the I-SPY 2 study [has] an adaptive design to identify potentially promising strategies to move them forward into phase 3 studies. It’s not designed to look at arms head to head, but to look at signals. In the HER2-positive cohort, the control arm is the paclitaxel with trastuzumab and pertuzumab followed by anthracycline with cyclophosphamide which would be administered either every 2 or 3 weeks. In this case, tucatinib was administered together with the taxane and dual HER2 blockade antibodies.

Investigators started out administering tucatinib at 300 mg once daily in the first 8 patients. Three of those patients experienced grade 3 hepatotoxicity and 2 experienced grade 3 diarrhea. That was a high toxicity rate at that dose level, so investigators subsequently [initiated] 2 additional cohorts, 1 [in which] tucatinib was administered at 250 mg once daily and [1 in which] tucatinib was administered in an adaptive fashion—150 mg once daily on days 1 to 28 and then 250 mg once daily on days 29 to 84 to complete the coadministration with paclitaxel.

Ultimately, the toxicity was very similar in those 2 subsequent arms. One patient of 5 in the 250-mg arm experienced grade 3 hepatotoxicity and 1 experienced grade 3 diarrhea. Among the 7 patients who participated in the adaptive tucatinib design, 2 experienced grade 3 hepatotoxicity and 2 experienced grade 3 diarrhea. So even with the dose reduction and adaptive strategy, there was unacceptable toxicity and ultimately that arm was suspended.

Investigators did not have pathologic CR data to present at the time of the meeting; they did, however, present some of the MRI substudy data. …Fifteen of the 17 patients had more than an 80% reduction in tumor volume by MRI, indicating that there were active responses to the prescribed regimen but again unacceptable toxicity.

**KAKLAMANI**

This is why we do clinical trials, right? This is a prime example of a trial really showing unacceptable toxicity with a combination of a taxane and tucatinib. I guess the investigators’ thought was, if you want to combine tucatinib with something, you want to combine it maybe with an antibody–drug conjugate but not with paclitaxel because of that toxicity. There are trials looking at tucatinib in the adjuvant setting to try to see whether we can actually move this drug forward.
Next-Generation Antibody-Drug Conjugates Make Their Mark in Breast Cancer

by JANE DE LARTIGUE, PhD

IN 2013, ADO-TRASTUZUMAB EMTANSINE (T-DM1; Kadcyla) gained FDA approval for the treatment of patients with HER2-positive metastatic breast cancer (MBC), making it the first antibody-drug conjugate (ADC) with an indication for a solid tumor. Since then, ADCs have become one of the fastest-growing classes of oncology drug therapy. In breast cancer, ADCs continue to evolve, with advancements in indications, targets, and drug designs (FIGURE). Recent developments in the field include full regulatory approval for sacituzumab govitecan-hziya (Trodelvy), a first-in-class Trop-2-targeted ADC for patients with metastatic triple-negative breast cancer (TNBC). Meanwhile, fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-targeted ADC initially approved in 2019, recently demonstrated superior efficacy to T-DM1 in previously treated patients with HER2-positive MBC, according to topline data from the DESTINY-Breast03 trial (NCT03529110). The honing of ADC design also may open new therapeutic doors. Because of their ability to deliver a membrane-permeable payload, sacituzumab govitecan and trastuzumab deruxtecan are able to kill nearby target antigen-negative tumor cells via the “bystander effect.” Partly because of this effect, investigators hypothesize that trastuzumab deruxtecan and other novel HER2-targeted ADCs may also prove effective in patients with breast cancer that is classified as HER2 low, for whom HER2-targeted therapy is not currently indicated. A growing number of ADCs are now in development in breast cancer, with a variety of novel designs, including several that are in late-stage clinical trials (TABLE). If these drugs continue to deliver on the promise they have demonstrated in earlier trials, then ADCs appear poised to further shape the breast cancer treatment landscape in coming years.

BREAST CANCER SUCCESS

Sometimes described as the “Trojan horses” of the cancer therapy armamentarium, ADCs have been in development for decades, with initial indications in hematologic malignancies. These drugs are composed of 3 major components: a monoclonal antibody (mAb) targeting a tumor-associated antigen, a cytotoxic drug (the “payload”), and a linker that connects them. T-DM1 is composed of the HER2-targeted mAb trastuzumab conjugated to emtansine, a potent inhibitor of tubulin polymerization, via a noncleavable linker. T-DM1 has a drug-to-antibody ratio (DAR) of 3.5, meaning that an average of 3.5 emtansine molecules are carried by each molecule of trastuzumab.

The initial T-DM1 approval, for the treatment of HER2-positive MBC, was based on results from the phase 3 EMILIA trial (NCT00829166). T-DM1 significantly improved median progression-free (PFS) and overall survival (OS) compared with the combination of lapatinib (Tykerb), a HER2/EGFR inhibitor, plus capecitabine (Xeloda), which inhibits DNA synthesis by reducing thymidine. Median PFS was 9.6 months with T-DM1 vs 6.4 months with lapatinib/capecitabine (HR, 0.55-0.77; \( P < .001 \)); median OS was 30.9 months with T-DM1 vs 25.1 months with lapatinib/capecitabine (HR, 0.68; 95% CI, 0.55-0.85; \( P < .001 \)). In the frontline setting, the MARIANNE trial (NCT01120184) demonstrated that T-DM1, either alone or combined with pertuzumab (Perjeta), also a HER2-targeted mAb, was noninferior to the combination of trastuzumab (Herceptin) and a taxane for the treatment of HER2-positive MBC. Noninferiority was based on median PFS data of 14.1 months with T-DM1 monotherapy, 15.2 months with T-DM1 plus pertuzumab, and 13.7 months with trastuzumab plus a taxane. Although superiority was not established, the novel combination generally was less toxic and provided a better quality of life.

Although the combination of pertuzumab, trastuzumab, and a taxane is the preferred regimen in this setting according to National Comprehensive Cancer Network Guidelines, T-DM1 provides a treatment option for patients for whom taxane therapy is unsuitable. In 2019, T-DM1 was approved for the adjuvant treatment of patients with HER2-positive early breast cancer following the KATHERINE trial (NCT01772472), in which T-DM1 improved invasive disease-free survival by 50% compared with trastuzumab (HR for invasive disease or death, 0.50; 95% CI, 0.39-0.64; \( P < .001 \)) in patients with residual invasive disease after neoadjuvant treatment with trastuzumab and a taxane. With an average of 8 deruxtecan molecules per antibody molecule, trastuzumab deruxtecan has a higher DAR than T-DM1. Historically, increasing the DAR of a drug has negatively affected its pharmacokinetic profile, but this was not the case for trastuzumab deruxtecan because of its ADGs, CONTINUED ON PAGE 88.

FIGURE. Timeline of FDA Approvals of ADCs for Breast Cancer

<table>
<thead>
<tr>
<th>Approval date</th>
<th>Approval</th>
<th>Drug</th>
</tr>
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<tbody>
<tr>
<td>FEBRUARY 2013</td>
<td>ADO-TRASTUZUMAB EMTANSINE (T-DM1)</td>
<td>HER2-positive MBC previously treated with trastuzumab and taxanes</td>
</tr>
<tr>
<td>MAY 2019</td>
<td>T-DM1</td>
<td>Adjuvant therapy in HER2-positive early breast cancer with residual disease after neoadjuvant therapy</td>
</tr>
<tr>
<td>DECEMBER 2020</td>
<td>FAM-TRASTUZUMAB DERUXTECAN-NXKI</td>
<td>HER2-positive advanced breast cancer previously treated with ≥ 2 prior anti-HER2-based regimens in the metastatic setting</td>
</tr>
<tr>
<td>APRIL 2021</td>
<td>SACITUZUMAB GOVITECAN-HZIYA</td>
<td>Metastatic TNBC in the third line and beyond</td>
</tr>
<tr>
<td>APRIL 2021</td>
<td>SACITUZUMAB GOVITECAN</td>
<td>Unresectable locally advanced or metastatic TNBC in the third line and beyond</td>
</tr>
</tbody>
</table>

ADC, antibody-drug conjugate; MBC, metastatic breast cancer; TNBC, triple-negative breast cancer.

*Accelerated approval.

via a linker that is selectively cleaved by lysosomal cathepsins. With an average of 8 deruxtecan molecules per antibody molecule, trastuzumab deruxtecan has a higher DAR than T-DM1. Historically, increasing the DAR of a drug has negatively affected its pharmacokinetic profile, but this was not the case for trastuzumab deruxtecan because of its ADGs.
Drug Designs

ADCs MAY OFFER THE BEST OF TWO WORLDS

by JANE DE LARTIGUE, PhD

IN GENERAL, ANTIBODY-DRUG CONJUGATES (ADCs) function by binding to their target antigen on the cell surface via their monoclonal antibody (mAb) component. They are then taken up into the cell in specialized compartments called endosomes, which bud off from the inner side of the plasma membrane. Once the ADC is inside the cell, the linker is degraded, releasing the payload to selectively kill cells that express the target antigen.1-4

Designing an effective ADC is highly complex because variations in any of the 3 components can significantly influence efficacy and toxicity. The choice of target antigen is key; ideally it should be a cell-surface protein that is either highly or exclusively expressed on cancer cells and is rapidly internalized to bring the ADC into the cell soon after binding.1

Most ADCs target well-established tumor-associated antigens against which other types of targeted therapies have also been designed. Some ADCs repurpose antibodies that have already achieved significant clinical success as naked mAbs, such as trastuzumab (Herceptin).5 Typically the antibody is immunoglobulin G (IgG) based and is fully human or humanized to minimize the potential for immunogenicity and maximize target specificity and half-life in the circulation (Figures).5

Although an ADC’s antitumor activity is primarily mediated by its payload, the mAb element can exert its own effects by promoting antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. Additionally, if the ADC targets an oncogene, such as HER2, the mAb may inhibit oncogene activation, thus suppressing downstream signaling. Antibody design can be manipulated to either exploit or minimize these effects.2,4

Payloads and Linkers

The payload is most commonly a chemotherapeutic agent, although areas of active exploration include alternatives such as immune-stimulating agents. Very few (<0.1%) ADC molecules actually make it into the target cell; thus, to overcome their effectively low concentrations, successful chemotherapeutic payloads generally must be much more potent than the drugs used for systemic therapy.2,4

Several distinct classes of chemotherapy have been employed. Microtubule-disrupting agents exert their effects by blocking mitosis, leading to cell cycle arrest, whereas DNA-alkylating agents and DNA topoisomerase inhibitors both induce irreparable DNA damage and cell death.2,4

Importantly, if the payload can pass freely across the cell membrane, it may be able to diffuse into neighboring tumor cells and exert its effects there too, regardless of whether those cells express the target antigen. This phenomenon is known as “bystander killing.”2,4

The linker plays a vital role in ensuring that the payload is released only at the appropriate time. Currently, most linkers can be classified as either cleavable or noncleavable. The former are designed to include chemical motifs that are targeted by specific degradative enzymes or that break down under certain cellular conditions, such as low pH. In contrast, noncleavable linkers are degraded along with the antibody when the endosomes fuse with the lysosome, the cell’s digestive organelle.1,2,4

In addition to the type of linker, the site of linker attachment and the number of drug molecules that are loaded onto a single antibody (drug-to-antibody ratio [DAR]) are important factors. In theory, the higher the DAR, the more potent the ADC, although in practice this is not so clear-cut.2,4

Conventional methods for generating ADCs randomly conjugate the payload to lysine residues on the antibody. However, due to the abundance of available lysine residues on an IgG molecule, this leads to a heterogeneous mix of ADCs with variable DARs. Conjugation to the relatively rarer available cysteine residues works better, but recently developed site-specific conjugation methods allow coupling of the payload to specifically defined or engineered sites within the antibody to dictate drug characteristics.5,7,8

For a full list of references, see the article at OncPathways.com.

FIGURE. Structure and Mechanism of Action of Antibody-Drug Conjugates4

The basic components of an antibody-drug conjugate (ADC), illustrated at left (A), are a humanized/human monoclonal antibody (mAb), a chemical linker, and a cytotoxic payload. The key steps in the mechanism of action for an ADC are illustrated at right (B).

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novel linker design.\textsuperscript{10,11,22} The deruxtecan payload of this agent is also much more membrane permeable than that of T-DM1; as a result, the potent bystander killing that trastuzumab deruxtecan demonstrates is absent from T-DM1.\textsuperscript{1,10}

Trastuzumab deruxtecan was granted accelerated approval in December 2019 based on the phase 2 DESTINY-Breast01 study (NCT03248492) for the treatment of patients with HER2-positive MBC who have received 2 or more prior HER2-targeted therapies in the metastatic setting.\textsuperscript{5} The novel agent demonstrated an objective response rate (ORR) of 60.9% (95% CI, 53.4%-68.0%) and a median duration of response (DOR) of 14.8 months (95% CI, 13.8-16.9).\textsuperscript{12}

Numerous clinical trials evaluating trastuzumab deruxtecan are ongoing, including a head-to-head comparison with T-DM1 in DESTINY-Breast03. Results from the primary analysis were first presented at the 2021 European Society for Medical Oncology Congress.\textsuperscript{4,5,22} Among the 524 patients randomized at data cutoff, trastuzumab deruxtecan significantly improved median PFS compared with T-DM1 (3.5), SYD985 has demonstrated higher antitumor activity in preclinical models.\textsuperscript{3,23} In the phase 3 TULIP trial (NCT03262935), SYD985 was approved against physician’s choice of therapy for the treatment of patients with previously treated HER2-positive MBC. SYD985 significantly improved median PFS (7.0 months vs 4.9 months; HR, 0.64; 95% CI, 0.49-0.84; \(P = 0.002\)). The most common adverse effects (AEs) in the SYD985 arm were conjunctivitis, keratitis, and fatigue.\textsuperscript{21}

Other notable HER2-targeted ADCs in development are ARX788, which has a tubulin inhibitor payload\textsuperscript{20}; ZW49, a bispecific ADC that employs

### ADCs With Targets Under Development in Breast Cancer

<table>
<thead>
<tr>
<th>ADC (manufacturer)</th>
<th>Payload (mechanism of action)</th>
<th>Development phase in breast cancer</th>
<th>Trial name (ClinicalTrials.gov identifier)</th>
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<tbody>
<tr>
<td>HER2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine\textsuperscript{a} (Genentech)</td>
<td>DM1 (MT inhibitor)</td>
<td>3</td>
<td>KATE3 (NCT04740918)</td>
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<tr>
<td>Fam-trastuzumab deruxtecan-muxi\textsuperscript{a} (AstraZeneca and Daiichi Sankyo)</td>
<td>Deruxtecan (DNA topoisomerase I inhibitor)</td>
<td>3</td>
<td>DESTINY-Breast02 (NCT03523585)\textsuperscript{a}</td>
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<tr>
<td>Vic-trastuzumab duocarmazine (Byondis)</td>
<td>DUBA (DNA-alkylating agent)</td>
<td>3</td>
<td>TULIP (NCT03262935)\textsuperscript{a}</td>
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<tr>
<td>ARX788 (Ambrx Biopharma Inc)</td>
<td>AS269 (MT inhibitor)</td>
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<td>ACE-Breast-03 (NCT04829404)</td>
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<tr>
<td>A166 (Klius Pharma)</td>
<td>Duo-5 (MT inhibitor)</td>
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<td>KliusPharma (NCT03602079)</td>
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<td>Sacituzumab govitecan-hlz\textsuperscript{a} (Gilead Sciences Inc)</td>
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<tr>
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<td>LIV-1</td>
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<tr>
<td>Ladiratuzumab vedotin (Seagen Inc)</td>
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<td>MORAb-202 (Eisai Co, Ltd)</td>
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<td>B7-H3</td>
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<td>MGCO18 (MacroGenics Inc)</td>
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<td>CD205</td>
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<tr>
<td>OBTO76 (Oxford BioTherapeutics Ltd)</td>
<td>DM4</td>
<td>1</td>
<td>OBTO76-001 (NCT04064359)</td>
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</tbody>
</table>

ADC, antibody-drug conjugate; DM1, ravtansine; DUBA, duocarmycin-hydroxybenzamide-azaindole; Duo-5, duostatin-5; FR, folate receptor alpha; MMAE/F, monomethyl auristatin E/F; MT, microtubule; PBD, pyrrolobenzodiazepine; ROR2, receptor tyrosine kinase-like orphan receptor 2; TLR7/8, Toll-like receptor 7/8.

\textsuperscript{a}Approved by the FDA for breast cancer indications.

\textsuperscript{b}Trial is ongoing but not actively recruiting participants.
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

To nominate, please visit: giantsofcancercare.com/nominate

PROGRAM OVERVIEW

- Nominations are open through February 28, 2022.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2022 inductees.
- The 2022 Giants of Cancer Care® class will be announced in spring 2022.

NO PURCHASE NECESSARY. Contest begins on or about November 4, 2021 at 12:01 a.m. ET and ends on February 28, 2022 at 11:59 p.m. ET. Open only to those who are 18 years of age or older at the time of entry and who are a licensed healthcare professional (i.e., MD, DO, PhD, and/or RN) working in the oncology space at the time of application and award. Subject to Official Rules. See Official Rules at www.giantsofcancercare.com for additional eligibility restrictions, prize descriptions, restrictions, and complete details. Odds of winning depend on the number of eligible entries received. Void where prohibited. Sponsor: Intellisphere, LLC.
an antibody targeting both the trastuzumab- and pertuzumab-binding sites on HER2 simultaneously; and BDC-1001, which uses a Toll-like receptor agonist as its payload and is designed to stimulate an antitumor immune response rather than directly kill tumor cells.26,27 ZW49 and BDC-1001 also both recently displayed promising preliminary activity in ongoing phase 1/2 clinical trials, according to the companies developing the drugs.26,27

ARX788 was highlighted in a presentation at 2021 SABCS, in the ACE-Breast-01 study (CTR20171162) in patients with heavily pretreated HER2-positive MBC, among 29 patients who received a dose of 1.5 mg/kg every 3 weeks, the ORR was 66% (95% CI, 45.7%-82.1%), the median DOR was 14.4 months (95% CI, 9.0 months—not reached), and the disease control rate (DCR) was 100%. Notably, the ORR was 80% among 5 patients previously treated with HER2-targeted ADCs. ARX788 was well tolerated, with mostly grade 1 or 2 AEs.28 ARX788 has been granted fast-track designation by the FDA in this setting.29

EXPANDING BEYOND HER2
An estimated 15% to 20% of breast cancers are classified as HER2 positive, with high levels of HER2 protein expression, defined as an immunohistochemistry (IHC) score of 3+, and/or HER2 gene amplification by in situ hybridization. Up to 50% are classified as HER2 low (IHC1+ or 2+, without gene amplification).3,10,15 An estimated 15% to 20% of breast cancers are HER2 positive, with high levels of HER2 protein expression, defined as an immunohistochemistry (IHC) score of 3+, and/or HER2 gene amplification by in situ hybridization. Up to 50% are classified as HER2 low (IHC1+ or 2+, without gene amplification).3,10,15

HER2 histology (IHC) score of 3+, and/or HER2 protein expression, defined as an immunohistochemistry (IHC) score of 3+, and/or HER2 gene amplification by in situ hybridization. Up to 50% are classified as HER2 low (IHC1+ or 2+, without gene amplification).3,10,15

A first-in-human study of SYD985 conducted in patients with metastatic solid tumors (NCT02227771) included 95 evaluable patients with MBC in dose-expansion cohorts. Results showed ORRs of 33% (95% CI, 20.4%-48.4%) in the HER2-positive cohort (n = 48); 28% (95% CI, 13.8%-46.8%) in the HER2-low, hormone receptor-positive cohort (n = 32); and 40% (95% CI, 16.3%-67.6%) in the HER2-low, hormone receptor-negative cohort (n = 15). All were partial responses (PRs).31

TROP-2 IN TNBC AND BEYOND
TNBCs do not express HER2; thus, alternative antigen targets are under investigation. Studies exploring Trop-2, a transmembrane glycoprotein that is overexpressed in breast cancer, have yielded sacituzumab govitecan.10

Sicituzumab govitecan is a first-in-class Trop-2-targeted ADC, in which a Trop-2 mAb is conjugated to SN-38, a topoisomerase I inhibitor, via a cleavable linker. Sacituzumab govitecan has a high DAR (7.6) and has been shown to display bystander killing in preclinical studies.10,15 The FDA granted an accelerated approval to sacituzumab govitecan in April 2020 for patients with TNBC previously treated with at least 2 regimens in the metastatic setting.24 The decision was based on results of the phase 1/2 IMMU-132-01 study (NCT01631552) in patients with advanced epithelial tumors, which enrolled 108 patients with previously treated metastatic TNBC. The ORR was 33.3% (95% CI, 24.6%-43.1%), the median DOR was 7.7 months (95% CI, 4.9-10.8), and the therapy was well tolerated.25

One year later, sacituzumab govitecan received full FDA approval based on recently published results from the confirmatory phase 3 ASCENT trial (NCT02574455).3 One data demonstrated that sacituzumab govitecan significantly prolonged median PFS (5.6 months vs 1.7 months; HR, 0.41; 95% CI, 0.32-0.52; P < .001) and median DOR (12.1 months vs 6.7 months; HR, 0.48; 95% CI, 0.38-0.59; P < .001) compared with chemotherapy in patients with metastatic TNBC who had received at least 2 prior standard chemotherapy regimens in the advanced or metastatic setting, including at least 1 taxane.5

High Trop-2 expression is frequently seen in multiple breast cancer subtypes,16 and the IMMU-132-01 study included a cohort of 54 patients with hormone receptor–positive/HER2-negative MBC who had received at least 2 prior standard chemotherapy regimens in the advanced or metastatic setting, including at least 1 taxane.5

Another member of the HER family of tyrosine kinase receptors, HER3, promotes the oncogenic activity of HER2. HER3 is overexpressed in breast cancers and is associated with poor prognosis and resistance to HER2-targeted and endocrine therapies.25-27

Patritumab deruxtecan (HER3-DxD) is a HER3-targeted ADC composed of the mAb patritumab conjugated to deruxtecan via a novel cleavable linker that allows a high DAR (8) without compromising the drug’s physiochemical properties.28 HER3-DxD demonstrated promising antitumor activity in an ongoing phase 1/2 study (NCT02980341) in patients with heavily pretreated hormone receptor–positive, HER2-negative MBC, regardless of whether HER3 expression was low or high, and was well tolerated.29

Meanwhile, results of an interim analysis of TOT-HER3 (NCT04610528), a window-of-opportunity study, revealed that a single dose of HER3-DxD (6.4 mg/kg) was associated with clinical response in patients with treatment-naive hormone receptor–positive, HER2-negative, primary operable breast cancer.30

Several other antigen targets are being explored for ADCs in breast cancer, including the LIV-1 protein and folate receptor-α, both of which are highly expressed in this cancer type. Ladirituzumab vedotin, which targets the former, and MORAb-202, which targets the latter, are both in the early stages of clinical development.6,42

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

Are you listening each week? Don’t miss the newest episodes.
Relapsed/Refractory Follicular Lymphoma Has a Bounty of Options in the Third Line

by BRITTANY LOVELY

SLOW DISEASE PROGRESSION IS often associated with low-grade follicular lymphoma. Despite the use of watch-and-wait approaches for the disease in early, low-grade stages, patients may eventually require treatment. “Patients live with this disease for generally 20 to 30 years and sometimes they need therapy,” Caron A. Jacobson, MD, MMSc, said in a recent OncLive Peer Exchange®.

Standard first-line treatment options for this population include front-line chemoimmunotherapy with R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone) or rituximab and bendamustine. However, data for some chemotherapy-free regimens, such as rituximab and lenalidomide (Revlimid), have demonstrated impressive results, and obinutuzumab (Gazyva) and lenalidomide demonstrated a 2-year progression-free survival (PFS) rate of 90%.

“Therapy is often very effective at causing the lymphoma to go into remission, but given enough time [the disease] is bound to relapse and patients will need subsequent therapies,” Jacobson said. “It has generally a very long natural history and because most people are 68 or 70 and older when [they receive their diagnosis], it’s a disease they’ll die with, not necessarily a disease they’ll die from.”

In the Peer Exchange discussion, Jacobson and a panel of hematologic experts talked about the evolving landscape for patients with relapsed or refractory follicular lymphoma. They highlighted updated findings presented at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition, during which data on PI3K inhibitors and chimeric antigen receptor (CAR) T-cell therapies provided new insights for sequencing therapies in this population.

INHIBITORS IN THE THIRD LINE AND BEYOND

The National Comprehensive Cancer Network guidelines indicate that patients may benefit from a period of observation following disease progression after first-line therapy. Preferred regimens for those patients are similar to those offered in the first line and include chemoimmunotherapy with anti-CD20 monoclonal antibodies, and either single-agent rituximab or rituximab in combination with lenalidomide.

For patients with more advanced relapsed or refractory disease, options in the third or later line of therapy are expanding, including several approved PI3K inhibitors (TABLE 1). “We have duvelisib [Copiktra], idelalisib [Zydelig], copanlisib [Aligoppa], and umbralisib [Ukoniq],” Jacobson said. “What’s been remarkable is that the PI3 kinases seem very consistent in terms of response rate, complete response rate, and durable remission rate. But the durable remission rate does tend to be just approximately 1 year.”
Desire the agents’ efficacy, confirmatory trials for both duvelisib and idelalisib have failed to support the continued approval for the treatment of patients with follicular lymphoma. In December 2021, Secura Bio, Inc, voluntarily withdrew duvelisib’s indication for use in patients with relapsed or refractory follicular lymphoma following at least 2 previous systemic therapies, stating that the competitive landscape for this population no longer merited the postmarketing requirements for the agent’s continued approval. Duvelisib had received accelerated approval in 2018.3

Idelalisib met a similar end in January 2022, when Gilead Sciences, Inc, announced its decision to remove the indications for patients with treat relapsed follicular lymphoma and relapsed small lymphocytic leukemia, both of which had been accelerated approvals.6 The company also cited the competitive landscape as playing a part in difficulties experienced during recruitment for the confirmatory trial.

In terms of distinguishing between the available options, toxicities may play a role in the decision. "The data with copanlisib are a little bit distinct," Brian T. Hill, MD, PhD, said. "It has some other unique toxicities—it can cause hyperglycemia and hypertension during the infusion—and does require weekly doses." Hill added that this information and the availability of other PI3K inhibitors have increased investigators’ knowledge base. "New dosing strategies are being explored with some of the newer agents [regarding] intermittent dosing, which likely are going to lead to better tolerability. One of the things that we’ve seen over the development of these agents is that most investigators and clinicians have [become] better at managing and being on the lookout for the toxicities, so that may be part of why we see lower grades with some of the newer agents."

That awareness fueled the decision to evaluate the efficacy of the PI3K inhibitor in combination with the well-established rituximab. The combination demonstrated superior efficacy to rituximab alone across patients with indolent non-Hodgkin lymphoma (NHL) in the phase 3 CHRONOS-3 study (NCT02367040). Investigators of the study compared copanlisib in combination with rituximab with placebo plus rituximab in patients with relapsed, advanced indolent NHL, including those with follicular lymphoma grades 1-3a, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, marginal zone lymphoma, and small lymphocytic lymphoma.8

Patients randomized to the copanlisib arm (n = 307) received the agent at 60 mg intravenously (IV) on days 1, 8, and 15 of a 28-day cycle. Patients in the copanlisib arm and those in the placebo arm (n = 151) received rituximab at 375 mg/m2 on days 1, 8, 15, and 22 during cycle 1, and on day 1 of cycles 3, 5, 7, and 9. The primary end point was PFS by central review. Select secondary end points included objective response rate (ORR), duration of response (DOR), and overall survival (OS). A majority of patients in both arms had follicular lymphoma histology at 59.9% and 54% with placebo. The CR rates among patients with follicular lymphoma grades 1-3a, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, marginal zone lymphoma, and small lymphocytic lymphoma were 34% vs 60.3%, respectively. Among patients with follicular lymphoma the ORR was 85% with copanlisib compared with 54% with placebo. The CR rates were 37% and 21%, respectively. Investigators noted safety signals were consistent with the known adverse effects for each agent and no new ones were observed.8

"This is really so far a very positive trial, showing that with the rituximab/copanlisib combination, there is a high response rate, a longer duration of response," Michael Wang, MD, said. "I hope that the overall survival will also be improved, [demonstrating] that rituximab with copanlisib is a very effective therapy." In June 2021, Bayer submitted a supplementary new drug application to the FDA for the investigational combination.4

Moderator Bijal Shah, MD, MS, asked the panel about the use of next-generation sequencing to guide treatment decisions. Hill pointed out that although it is not routinely done in the front line, sequencing to determine EZH2 mutations or p53 in the relapsed setting is information worth pursuing. "I do think that it’s worth knowing the EZH2 status of any [patient with] relapsed follicular lymphoma, and that’s something that is routinely available or can be sent out [as] EZH2 is included on some of the panels that are available from Foundation Medicine and other groups," Hill said. "You may sometimes get other information—p53 or other things—from those panels that, again, might sort of sway you in one direction or the other."

EZH2 mutations represent an actionable mutation in relapsed or refractory disease. Specifically, patients may be eligible for treatment with tazemetostat (Tazverik) approved in the third-line setting for the treatment of patients with relapsed or refractory follicular lymphoma. Supporting the decision were data from the 2 single cohorts of a multicenter trial (NCT01897571). Among 42 patients the ORR was 69% (95% CI, 53%-82%), with a 12% CR rate and a 57% partial response rate.10

CAR T-CELL THERAPIES PUSH REMISSION RATES HIGHER

In addition to the expanded offerings for patients afforded by the advent of several PI3K inhibitors, the approved cellular therapy axicabtagene ciloleucel (axi-cel; Yescarta) has continued to demonstrate promise for patients with relapsed or refractory follicular lymphoma. "I certainly think transplant is a reasonable approach, [but]
I’ve never been doing as many autologous transplants in follicular lymphoma as I used to,” Ian W. Flinn, MD, PhD, said. “I’m much more excited about the potential for CAR T cells in this setting.”

Long-term follow-up data from the single-arm, phase 2 ZUMA-5 trial (NCT01105336) were presented at the 2021 ASH meeting.11 In the trial, patients with indolent NHL who had previously received 2 or more lines of systemic therapy, including treatment with an anti-CD20 monoclonal antibody and an alkylating agent, received axi-cel at 2 × 10^6 CAR T cells/kg. The primary end point was ORR per national SCHOLAR-5 external control cohort (Table 2).12

“ZUMA-5 was superior to other available therapeutic options in terms of response rate, complete response rate, time to next treatment, and time to treatment failure,” Jacobson said. “But most importantly the data were statistically significantly superior in terms of 3-year OS, which was a shock. No one thought that you could see an OS benefit in follicular lymphoma.”

Jacobson noted that she would add an asterisk to the data because they are not from a randomized trial. However, she added, “these are probably the best data we have that supports using CAR T-cell therapy for patients in this advanced line of therapy.”

### Table 2. Outcomes from SCHOLAR-5 Vs ZUMA-5 Analysis

<table>
<thead>
<tr>
<th>Outcome analysis: ≥ 3 prior lines of therapy</th>
<th>SCHOLAR-5 (n = 85)</th>
<th>ZUMA-5 (n = 86)</th>
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<tr>
<td>ORR</td>
<td>49.4%</td>
<td>94.2%</td>
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<tr>
<td>Median OS, months (95% CI)</td>
<td>59.8 (21.9-NR)</td>
<td>NR (39.6-NR)</td>
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<td>24-month OS rate (95% CI)</td>
<td>63.4% (50.3%-76.4%)</td>
<td>81.2% (71.2%-88.1%)</td>
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<tr>
<td>Median PFS, months (95% CI)</td>
<td>12.7 (6.2-14.7)</td>
<td>39.5 (25.7-NR)</td>
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<tr>
<td>24-month PFS rate (95% CI)</td>
<td>15.0% (4.8%-25.2%)</td>
<td>63.4% (51.6%-73.0%)</td>
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<th>Subgroup analysis: ≥ 4 lines of prior therapy</th>
<th>SCHOLAR-5 (n = 59)</th>
<th>ZUMA-5 (n = 60)</th>
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<tr>
<td>ORR, objective response rate, OS, overall survival, DFS, progression-free survival.</td>
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</table>

To compare expectations across therapies, Jacobson and colleagues conducted an analysis comparing the outcomes from ZUMA-5 with those from other agents that patients with follicular lymphoma may have received in a similar setting, using a weighted sample from the international SCHOLAR-5 external control cohort (Table 2).12

“SCHOLAR-5 was a combination of retrospective reviews of modern third-line approaches for follicular lymphoma at a number of international sites in Europe and in the United States,” Jacobson explained. “It also included data from the DELTA trial [NCT01282424] of idelalisib in this line of therapy. Investigators performed propensity score weighting to match the patients enrolled in ZUMA-5,” she said, adding that patients were very closely matched in terms of the known risk observed in this histology.

In total, 85 patients were included in the SCHOLAR-5 cohort. The ORR among these patients was 49.9% vs 94.2% for those treated with axi-cel in ZUMA-5 (odds ratio, 16.2; 95% CI, 9.0-30.0; P < .001). The median PFS was 12.7 months (95% CI, 6.2-14.7) vs 39.6 months (95% CI, 25.7-NR) in the SCHOLAR-5 and ZUMA-5 cohorts, respectively (HR, 0.28; 95% CI, 0.28-0.95; P = .033).

The median OS was 59.8 months (95% CI, 29.1-NR) vs NR (95% CI, 39.6-NR) in the SCHOLAR-5 and ZUMA-5 cohorts, respectively (HR, 0.43; 95% CI, 0.23-0.81; P = .010).

### References

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