Triplet and Quadruplet Regimens Set a New Course for Myeloma

PEER EXCHANGE
SIMBA Therapy Encounters Barriers But Holds Promise for Neutropenia

OncPathways
Next Steps for KRAS Inhibitors Focus on Tackling Resistance

63rd ASH Annual Meeting
Cilta-Cel Continues to Demonstrate Promise Across Malignancies
Updates on Dose Adjustments for Patients With CLL/SLL
A New Standard Emerges for Patients With DLBCL

Clinical Trial in Focus
CD166 Represents a New Avenue of Attack for Breast Cancer

Dana-Farber Cancer Center
Overcoming Barriers to Clinical Access in Oncology Care Delivery Requires Multilevel Interventions

By Christopher S. Lathan, MD, MS, MPH

In Memoriam
Honoring the Legacy of Healthcare Giant Michael J. Hennessy Sr

OncLive.com
Bringing the Global Oncology Community Together
**ARE YOU THINKING DEEP ENOUGH IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?**

**Relapse is expected, but deep response could be too**

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

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

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

*Visit [ThinkDeepMM.com](http://ThinkDeepMM.com)*

**References:**

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

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The absence of minimal residual disease has served as a benchmark for investigators exploring new treatment options for patients with newly diagnosed myeloma. Combination regimens have stepped into focus as new agents are tacked onto backbone therapy. A leading investigator in the field, Marc J. Braunstein, MD, PhD, provides an overview of the landscape in his expert commentary.

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Bridging the Technological Gap in Oncology Patient Care

AS WE APPROACH THE 2-year mark of the COVID-19 pandemic, it has become apparent that changes in the delivery of oncology care are here to stay. Rises in telehealth visits are only the tip of the iceberg in terms of patient preference and practices are going to be hard-pressed to integrate new technology standards in the coming months and years.

Results of a survey conducted by PatientPop and presented as part of a Physician Bootcamp sponsored by OncologyLive’s sister site, Medical Economics®, showed that patients prefer having an active role in their health care. This includes the ability to self-schedule appointments online and have access to forms ahead of in-office or telehealth visits.1 Specifically, the survey reported that 51% of patients booked appointments online rather than calling a practice and 36% of those appointments were scheduled after office hours.1

“Health care is one of the last major industries to be transformed by technology,” Luke Kervin, co-founder and CEO of PhysicianPop said in the discussion. “[Although] electronic health records are well known to [those in practices], they are relatively invisible to patients and provide none of the consumer-oriented conveniences patients want from their doctors.” These pandemic-influenced changes may open the door for investigators to push the boundaries of how technology can ease burdens in other care settings. For example, in this issue’s Oncology Business Management section, Douglas E. Holt, MD, a radiation oncologist at Gamma West Cancer Services in Idaho Falls, Idaho, explores how virtual reality (VR) may offer an alternative method of imaging review for patients with cancer.

“Patients struggle to know what’s happening within their own bodies,” said Holt. “They’re making decisions being somewhat or quite uninformed about what’s going on. VR [provides] an opportunity to help patients be engaged in their own disease process and on decisions of the future of their cancer [journey].” Holt recently was awarded the 2021 Association of Community Cancer Centers (ACCC) Innovator Award for his work developing a program with the aim to address the disconnect in patient education in oncology using VR. The goal of the proof-of-concept study was to identify and address the technical challenges of implementing VR in the clinic and to objectively measure subjective patient experiences with the technology.2

As new technologies begin to take shape in oncology practices, OncologyLive® and Medical Economics® will continue to deliver key updates that will help you stay ahead of the curve. If there are any areas that you would like to see more focus on in the coming months, please contact managing editor Brittany Lovely at blovely@mjh lifesciences.com.

REFERENCES
Cardinal Health™ Navista™ TS

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Scan the QR code or visit cardinalhealth.com/navista to learn more and request a demo.
Mike Hennessy was the beloved chairman and founder of MJH Life Sciences®, parent company of OncologyLive®. Hennessy’s multimedia endeavors have resulted in the transmission of vital clinical updates to health care audiences including practicing clinicians, nurses, patients, and caregivers, have improved outcomes for countless number of patients.

Hennessy spent his career turning his passion for building businesses and creating jobs into a run of successful ventures and brands. Following his graduation from Rider University in 1982, he started his career in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, Hennessy became chief operating officer of Medical World Business Press, which was part of the launch of medical newspapers and other media products. The company prospered and was eventually sold to a Boston, Massachusetts-based venture capital firm.

Hennessy launched Multimedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, Inc., acquired Multimedia HealthCare, about the time that Hennessy was pioneering a new approach to print and digital publishing with Intellisphere®, LLC (now part of MJH Life Sciences®). Guided by the principles of innovation and entrepreneurial spirit, and reflecting its founder’s dedication to improving quality of life through health care research and education, Intellisphere publishes a variety of integrated print and digital products focusing on a range of topics in research and clinical medicine.

To build a comprehensive multimedia and education platform, Hennessy added more companies and capabilities to the MJH Life Sciences™ portfolio. In 2004, he acquired Healthcare Research Analytics (HRA®), which has been the leader in health care market research for over 30 years. In 2005, Hennessy acquired ArcMesa Educators, LLC, leaders in online certification for pharmacy professionals. Reflecting his lifelong interest in politics, Hennessy acquired Campaigns & Elections magazine in 2005, publishing the journal through Political World Communications, LLC. He sold the publication to Biteback Media Ltd in 2011.

In February 2008, Hennessy acquired the rights to the journals Pharmacy Times® and The American Journal of Managed Care®, both recognized in their respective markets as authoritative, trusted media platforms that provide essential information to a large audience of health care professionals.

In April 2011, MJH Life Sciences® acquired Physicians’ Education Resource®, LLC (PER®), an accredited continuing medical education company that is an industry leader in producing high-quality, first-rate oncology and hematology meetings and conferences. The PER® acquisition included a variety of multichannel enduring educational activities, as well as the rights to legacy medical meetings, such as the annual Miami Breast Cancer Conference®.

Hennessy’s commitment to improving the lives of patients with cancer is deeply rooted within the halls of MJH Life Sciences®. As a complement to the industry-leading OncLive® platform, he developed the Giants of Cancer Care® awards to recognize the leaders and pioneers who often go unrecognized for their contributions to advancing oncology care. He further strengthened his commitment to education by acquiring CURE Media Group in 2014, followed by the purchase of the Chemotherapy Foundation Symposium, in his quest to provide oncology professionals with focused education on innovative cancer therapy.

In 2019, MJH Life Sciences® made its largest acquisition to date when it acquired the Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as Medical Economics® to its already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America. In addition to acquisitions, Hennessy organically developed ancillary in-house agency divisions with Proximyl Health®, Truth Serum NTWK, and MJH Global Medical Affairs.

Later in 2019, Hennessy elevated his own role to chairman while naming his son Mike Hennessy Jr to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr’s leadership, the company enhanced its global potential by entering into a long-term partnership with BDT Capital Partners, LLC in November 2021.

Because of his broad business and educational experience and understanding of the challenges facing New Jersey, Hennessy’s counsel and insight had been sought by several organizations, including his alma mater Rider University, where he served on the Board of Trustees and was elected to the executive committee. In addition to being active in state and national politics, Hennessy also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy’s true passion was his relationship with his wife, Patrice “Patti” Hennessy. After they met in college, Hennessy devoted his life to Patti and his family, raising 4 wonderful children, Shannon, Ashley, Mike Jr, and Chris. Hennessy was Patti’s rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University to expand the Science and Technology Center at their alma mater. The Mike & Patti Hennessy Science and Technology Center is set to be completed in 2022.

Hennessy’s legacy and “family first” mantra will live on through his children; their spouses, Matt, Phil, Rachel, and Jordan; and his 10 grandchildren. He will be greatly missed by his family, friends, and his MJH Life Sciences family.
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Contact Syndax directly at [clinicaltrials@syndax.com](mailto:clinicaltrials@syndax.com)

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, KMT2Ar = lysine (K) methyltransferase 2A rearranged, MLLr = mixed lineage leukemia rearranged, MPAL = mixed phenotype acute leukemia, mNPM1 = nucleophosmin 1 mutation, R/R = relapsed/refractory.

Reference note: the content in this ad is attributed to data on file. Syndax Pharmaceuticals, Inc.
Implications of FDA Approval of Alzheimer Drug May Extend to Novel Anticancer Therapies

by MAURIE MARKMAN, MD

"It is not inconceivable that the serious deficiencies associated with the aducanumab approval process may be used in the future by critics of the accelerated approval pathway to deter use of this strategy in oncology."

T IS DIFFICULT TO KNOW where exactly to begin this commentary regarding the FDA approval to permit commercial sales of the Alzheimer disease drug aducanumab-avwa (Aduhelm). There are so many disturbing features of this story, with likely more to be told in the near future.

A reasonable starting point is to acknowledge that similarities of the regulatory process used to move this agent from the realm of objectively monitored investigative efforts designed to demonstrate both the safety and efficacy of the drug to the arena of sales and marketing to those increasingly and most often employed to permit quicker access of novel anticancer pharmaceutical agents. Therefore, it is not inconceivable that the serious deficiencies associated with the aducanumab approval process may be used in the future by critics of the accelerated approval pathway to deter use of this strategy in oncology.

In fact, the objective parameter of progression-free survival, commonly employed as a primary end point in many clinical trials, recognizes that cancer is increasingly viewed as a chronic illness in several settings. As a result, patients may appropriately follow multiple therapeutic strategies after they have progressed on a specific regimen in a trial. This makes it difficult if not impossible to conclude whether a particular investigative treatment delivered months or even years before a patient’s death was responsible for the overall survival outcome. This surrogate end point directly related to extending the time until a patient’s disease progresses is widely recognized as being clinically meaningful; however, many prominent academics still fail to appreciate, or simply refuse to consider, this critical point. For example, authors of a recent commentary on anticancer agents argued that “paying full price for products that have not been shown through randomized clinical trials to improve cancer survival or patients’ quality of life constitutes inefficient care.”

A POTENTIALLY DANGEROUS REGULATORY ROAD MAP

What are the specific concerns surrounding regulatory approval of aducanumab? The first to be highlighted is the use of a particular surrogate end point that was claimed by the company and advocates within the FDA to likely predict for a favorable clinical outcome. In this situation the FDA “based its decision on the effects of aducanumab on brain β-amyloid levels as a surrogate marker of reasonably likely clinical benefit.” Unfortunately, there remains considerable controversy regarding the relationship between this biological marker and specific disease-related symptoms or evidence of progression of Alzheimer disease. As a result, the relevance of this factor as a reliable and accurate clinically meaningful end point is highly questionable.

In fact, of the 11 members of the FDA advisory committee who were asked to consider approval of this agent for commercial use based on the presented data, 10 voted no and 1 voted uncertain regarding whether it was appropriate to conclude that this agent favorably affected the characteristic decline in cognitive function observed in this devastating neurological condition. The FDA’s subsequent approval of the agent despite the overwhelming vote to not support this action led to the unprecedented resignation of several members of the regulatory agency’s advisory committee.

The second concern with the approval regarded the overall safety findings of aducanumab, which demonstrated questionable clinical activity. Of the 3285 participants in registration-quality clinical trials evaluating aducanumab in
patients with early Alzheimer disease, approximately one-third of patients experienced brain edema and one-quarter experienced distressing symptoms, including headache, confusion, nausea, and dizziness. Subjective and objective toxic effects are commonly observed with anticancer agents, and their potential effect on a patient’s quality of life must be balanced against meaningful evidence of efficacy. Based on the data presented publicly to date, it is quite difficult to argue aducanumab satisfied this critical evaluation.

The next issue to be highlighted is the apparent lack of appropriate representation within the clinical trials of individuals who would potentially be eligible in the real world to receive aducanumab once commercially available. The authors of one report that examined the medical claims from the Centers for Medicare & Medicaid Services (CMS) found that rather remarkably the clinical trials of aducanumab would have excluded 92.2% of individuals with Alzheimer-related disorders, 91% with mild dementia due to Alzheimer disease, and 85.5% with mild cognitive impairment or mild dementia based on a single exclusion criterion. Further findings noted that most patients would meet multiple exclusion criteria. For example, individuals would have been excluded for the presence of common medical conditions, including cardiovascular disease, receiving anticoagulation, chronic kidney disease, and age greater than 85 years. In addition, the studies included a low percentage of Hispanic, Black, and Native American participants.

How relevant would the clinical trial data concerning both safety and efficacy leading to regulatory approval be for this agent when employed in the large population of individuals in the United States with Alzheimer disease and other forms of dementia? Finally, it is important to note the cost of aducanumab as set by the manufacturer: $56,000 per year. This does not include the price for tests (eg, brain MRI) to routinely monitor for associated toxicities of the agent, physician interactions, or required hospitalizations/emergency department visits associated with adverse effects. It should also be noted that the nonprofit Institute for Clinical and Economic Review suggested a value-based price of between $2500 and $8300 per year based on the available efficacy and toxicity data.

Concern by Medicare administrators was so great for the effect of the cost of this agent to the entire program that they have raised the cost of premiums for Medicare participants by 13% for 2022, despite the fact CMS has yet to determine whether it will agree to pay for this agent.

Clearly, there are serious issues to be considered here, and members of the cancer community can only hope this serious FDA misadventure will not negatively affect future access of patients with cancer to novel pharmaceutical agents.

REFERENCES

**FDA DIGEST**

### Subcutaneous Daratumumab Combination Moves Forward for Multiple Myeloma

The FDA has approved daratumumab and hyaluronidase-fihj (Darzalex Faspro) plus carfilzomib (Kyprolis) and dexamethasone (Kd) for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

The approval of the subcutaneous formulation of daratumumab plus Kd was supported by efficacy data from a single-arm cohort of the PLEIADES trial (NCT03412565), which showed that the combination produced response rates similar to those reported with intravenous daratumumab (Darzalex) plus Kd in the phase 3 CANDOR trial (NCT03158688).

Distinctively, in a single-arm cohort of 66 patients, the novel regimen elicited an 84.8% (95% CI, 73.9%-92.5%) overall response rate and a 77.3% very good partial response rate or better at a median follow-up of 9.2 months.

Additionally, the median duration of response with the regimen had not yet been reached. An estimated 85.2% (95% CI, 72.5%-92.3%) of patients continued to respond to treatment for at least 6 months, and an estimated 82.5% (95% CI, 68.9%-90.6%) of patients maintained response for at least 9 months.

To read more, visit [bit.ly/3GcqneL](bit.ly/3GcqneL).

### Sirolimus Protein-Bound Particles Gains Approval for Malignant PEComa

The FDA has approved sirolimus albumin-bound particles (Fyarro) for injectable suspension for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

The decision was based on findings from the phase 2 registrational AMPLECT trial (NCT02494570). Assessment by a blinded independent central review showed that the objective response rate was 39% (n = 12 of 31), with 2 patients achieving a complete response during the follow-up period.

The long-term median duration of response had not yet been reached (95% CI, 6.5 months-not estimable) at a median follow-up of 36 months. Among those who responded to treatment, 92% experienced a response that lasted for at least 6 months, 67% achieved a response lasting for at least 12 months, and 58% had a response lasting at least 2 years.

To read more, visit [bit.ly/3sHsZOG](bit.ly/3sHsZOG).

### Decision Date Is Pushed Back for Pacritinib in Myelofibrosis, Severe Thrombocytopenia

The FDA has extended the review period for the new drug application (NDA) for pacritinib, for use in adult patients with intermediate-risk or high-risk primary or secondary (postpolycythemia or postessential thrombocytosis) myelofibrosis and severe thrombocytopenia with a baseline platelet count of 50 × 10^9/L. The FDA protracted the Prescription Drug User Fee Act (PDUFA) action date by 3 months to February 28, 2022.

The application was previously granted priority review designation with an action date of November 30, 2021. CTI BioPharma, the developer of the agent, noted that the regulatory agency previously requested additional clinical data, which they submitted on November 24, 2021. The FDA informed the company that “it considers the data submission to constitute a ‘major amendment’ to the NDA. Therefore, the PDUFA date has been extended by 3 months to provide additional time for a full review of the submission.”

The NDA was based on data from the phase 3 PERSIST-1 (NCT01773187) and PERSIST-2 (NCT02055781) trials, and the phase 2 PAC203 trial (NCT04884191). Of the patients who received the agent in the PERSIST-2 study, 29% (n = 22 of 74) experienced a reduction in spleen volume of at least 30% vs 3% (n = 2 of 72) of those who received the best available therapy (BAT) that included ruxolitinib (Jakafi). Moreover, 23% (n = 17) of patients in the pacritinib arm experienced a reduction in total symptom scores of at least 50% compared with 13% (n = 9) of patients in the BAT arm.

To read more, visit [bit.ly/3EnrCHI](bit.ly/3EnrCHI).

### ODAC to Convene for Ublituximab Plus Umbralisib in CLL/SLL

The FDA has scheduled a meeting of the Oncologic Drugs Advisory Committee (ODAC) in March or April 2022 to review the pending biologics license application/supplemental new drug application for ublituximab plus umbralisib (Ukoniq; U2) for use in adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The regulatory agency was initially expected to make a decision by March 25, 2022.

Intended discussion points for the meeting are the benefit-risk of the U2 combination for the treatment of patients with CLL/SLL and of U2 in relapsed/refractory marginal zone lymphoma or follicular lymphoma, along with the overall safety profile of the U2 regimen in data from the phase 3 UNITY-CLL trial (NCT02611231).

The call for the meeting is based on the agency’s concerns of an early analysis of overall survival (OS) data, according to TG Therapeutics, Inc, the developer of both agents. Specifically, as of the data cutoff of September 2021, the preliminary OS analysis demonstrated an imbalance that favored the control arm with an HR of 1.23, which was not statistically significant. However, when deaths related to COVID-19 were removed, the arms were balanced (HR, 1.04). The company said it will continue to evaluate this end point and the effect of COVID-19 on the results.

In previously reported data, the primary end point of the study of progression-free survival (PFS) was met. Patients treated with U2 had a median PFS of 31.9 months compared with 17.9 months for those in the control arm who received obinutuzumab (Gazyva) plus chlorambucil (HR, 0.546; \( P < .0001 \)).

To read more, visit [bit.ly/3ddZwT1](bit.ly/3ddZwT1).
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.
FDA Greenlights Adjuvant Pembrolizumab for Stage IIB or IIC Melanoma Following CR

THE FDA HAS APPROVED pembrolizumab (Keytruda) for the adjuvant treatment of adult and pediatric patients with stage IIB or IIC melanoma following complete resection (CR). The FDA also expanded the indication for the immunotherapy for adjuvant use in patients with stage III melanoma following CR to include pediatric patients 12 years and older.1

The indication for the agent’s use in patients with stage IIB and IIC melanoma is based on findings from the first interim analysis of the phase 3 KEYNOTE-716 trial (NCT03553836), in which pembrolizumab resulted in a statistically significant improvement in recurrence-free survival (RFS), reducing the risk of disease recurrence or death by 35% (HR, 0.65; 95% CI, 0.46-0.92; P = .0132) vs placebo. Specifically, the median RFS was not reached in either treatment arm.2

The 12-month RFS rate was 90.5% in the pembrolizumab arm compared with 83.1% in the placebo arm. In an analysis of key subgroups, pembrolizumab was favored over placebo with the greatest benefit observed in those with T3b (HR, 0.44; 95% CI, 0.24-0.80) and T4a (HR, 0.43; 95% CI, 0.18-1.04) disease.

After a median follow-up of 14.4 months, 11% (n = 54/487) of patients who received the immunotherapy experienced a recurrence or died vs 17% (n = 82/489) of those who were given placebo. Among those who experienced recurrence with pembrolizumab, 4.7% had distant recurrence and 6.4% had skin and/or lymph node regional recurrence. These rates were 7.8% and 8.4%, respectively, among those who received placebo.

Efficacy in pediatric patients, who were 12 years and older and had stage IIB, IIC, and III melanoma is supported by extrapolation of efficacy findings from adults, given similar biology and pharmacology of drug effect, as well as similar exposure-response for efficacy and safety.

“The standard of care for patients with resected stage IIB and IIC melanoma has been observation, despite the fact that for these patients, the risk of recurrence is nearly the same as for patients with later-stage disease for whom treatment is recommended,” Jason Luke, MD, director of the Cancer Immunotherapeutics Center at University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center in Pennsylvania, stated in a press release. “Today’s approval of pembrolizumab for the adjuvant treatment of patients 12 years and older with stage IIB and IIC melanoma following complete resection is an important advance that provides these patients with a new option that can help reduce the risk of their cancer returning.” Luke is also an associate professor of medicine at UPMC.

The multicenter, double-blind, placebo-controlled phase 3 trial enrolled a total of 976 patients with completely resected stage IIB or IIC melanoma. Study participants were randomized to receive 200 mg of pembrolizumab or the pediatric dose of 2 mg/kg every 3 weeks or placebo for up to 1 year until either recurrence or intolerable toxicity. Patients were stratified based on the American Joint Committee on Cancer’s AJCC Cancer Staging Manual, eighth edition, T stage (> 2.0-4.0 mm with ulceration vs > 4.0 mm without ulceration vs > 4.0 mm with ulceration).

The main efficacy outcome measure for the trial was investigator-assessed RFS.

“A really important aspect of this trial is that it has 2 parts: The first part is the adjuvant treatment, and the second part is the crossover,” Luke said in an interview with OncologyLive®. “Following patients and seeing what happens to them after they have recurrence events and go on to other therapies is an absolutely essential part of this clinical trial. [This way] we can better understand the long-term implications of these clinical data and what happens to these patients in these scenarios because we haven’t had this before.”

Regarding safety, adverse effects (AEs) that were reported in those with stage IIB or IIC melanoma were comparable to those reported in 1011 patients with stage III melanoma from the phase 3 KEYNOTE-054 trial (NCT02362594) and the 2799 patients with melanoma or non–small cell lung cancer treated with the immunotherapy as a monotherapy.1

Specifically, among the 483 patients evaluable for safety in the pembrolizumab arm, 93.0% experienced any-grade AEs, 79.9% of which were treatment related. Grade 3/4 AEs were reported among 15.3% of patients in the pembrolizumab arm, and 15.3% of patients discontinued treatment due to an AE. The most commonly reported treatment-related AEs in this arm were hypothyroidism, diarrhea, fatigue, pruritis, and rash.2

Among the 486 patients in the placebo arm, 89.1% experienced AEs of any grade, and 60.9% were treatment related. Grade 3/4 AEs occurred among 4.3% of patients, and a low rate (2.5%) of AEs were attributed to treatment discontinuation. The most commonly reported AEs in this arm were diarrhea, fatigue, asthenia, myalgia, and pruritis.2

“There were some naysayers when we started this trial [who said] that [patients with] stage IIB and IIC disease were too low risk to treat in a clinical trial,” Luke said. “I think these results really emphasize that patients with [those disease] stages truly are at high risk for rapid and distant metastatic recurrence. Treatment with pembrolizumab improves that situation quite substantially. I think [that] this treatment should be offered to all patients with stage IIB and IIC and [that] we should stop thinking about nonmodal melanoma as low risk; in fact, it is high risk and these patients deserve the opportunity to be treated.”

REFERENCES
Mechanism of action
- Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

How supplied
- 100 mg/4 mL (25 mg/mL) solution in a single-dose vial

Dose
- Adult patients:
  - 200 mg every 3 weeks or 400 mg every 6 weeks
  - Pediatric patients 12 years and older:
    - 2 mg/kg (up to 200 mg) every 3 weeks

Company: Merck

PIVOTAL CLINICAL TRIAL
KEYNOTE-716 (NCT03553836) was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial evaluating adjuvant pembrolizumab vs placebo in patients with completely resected stage IIB or IIC melanoma. Patients were randomly assigned 1:1 to receive pembrolizumab or placebo every 3 weeks for up to 17 cycles. Patients with confirmed recurrence were eligible for rechallenge with pembrolizumab or cross over to pembrolizumab if they received placebo.

Efficacy in the Keynote-716 Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab (n = 487)</th>
<th>Placebo (n = 489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFS</td>
<td>NR (22.6-NR)</td>
<td>NR (NR-NR)</td>
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<tr>
<td>Median in months (95% CI)</td>
<td>HR, 0.65; 95% CI, 0.46-0.92; P = .0132</td>
<td></td>
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<tr>
<td>Patients with event</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>Skin and/or lymph node regional recurrence</td>
<td>6.4%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>4.7%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

NR, not reached; RFS, recurrence-free survival.

Warnings and Precautions
- Immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic hematopoietic stem cell transplantation
- Embryo-fetal toxicity

Select Adverse Effects in the Keynote-716 Study

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Pembrolizumab (n = 483)</th>
<th>Placebo (n = 486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>93%</td>
<td>89.1%</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>79.9%</td>
<td>60.9%</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>16.1%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>15.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Led to death</td>
<td>0%</td>
<td>0%</td>
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</tbody>
</table>

Adverse effects of interest
- Hypothyroidism, hyperthyroidism, colitis, adrenal insufficiency, hepatitis, hypophysitis, infusion reactions, myasthenic syndrome, myositis, nephritis, pancreatitis, pneumonitis, sarcoidosis, severe skin reactions, and thyroiditis.

References
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 patients1-3

Consistent results with or without prior adjuvant chemotherapy2+

• Patients in the ADAURA trial are treated with ORAL TAGRISSO FOR 3 YEARS or until disease recurrence or unacceptable toxicity3

*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.1
†Control arm=placebo.
‡Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40).
CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; L858R, exon 21 leucine 858 arginine substitution; NE, not estimable; NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

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

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OVERWHELMING EFFICACY

ADJUVANT TAGRISSO: DELIVERING FOR RESECTABLE EGFR m NSCLC

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients1-3

The first and only EGFR TKI to help prevent disease recurrence or death in NSCLC, non-small cell lung cancer; QoL, quality of life; TKI, tyrosine kinase inhibitor.

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

TAGRISSO if ILD is confirmed

respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue

as detected by an FDA-approved test

NSCLC (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations,

or unacceptable toxicity1

Primary endpoints were DFS in the overall population (stage 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.1,2

Find out more at www.TagrissoResults.com

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.1,2

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 electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop 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

TAGRISSO® (osimertinib) tablets, for oral use

TREATMENT OF INTERSTITIAL LUNG DISEASE/ PNEUMONITIS

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Cardiac

Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Contact dermatitis

Includes dizziness, vertigo, and vertigo positional.

It is recommended to initiate treatment with an oral tablet of 240 mg after

Table 1. Recommended Dosage Modification for TAGRISSO

Target Organ

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc interval ≥ 600 ms or more than 2 separate ECGs</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>QTc interval ≥ 60 ms and less than 2 separate ECGs</td>
<td>Without TAGRISSO until QTc interval is less than 500 ms or recovers to baseline if baseline QTc interval is greater or equal to 480 ms; then resume at 40 mg dose</td>
</tr>
<tr>
<td>Symptomatic cognitive impairment</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>Without TAGRISSO until corrected.</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>Without TAGRISSO for up to 2 weeks.</td>
</tr>
<tr>
<td>Adverse reaction of Grade 3 or greater severity</td>
<td>Improvement to Grade 0-2 within 3 weeks.</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Without TAGRISSO for up to 2 weeks.</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Improvement to Grade 0-2 within 3 weeks.</td>
</tr>
</tbody>
</table>

Other [see Adverse Reactions (3.2) in the full Prescribing Information]

Adverse reactions reported in clinical trials were also observed in clinical trials involving patients with EGFR T790M mutation-positive NSCLC

Table 2. Adverse Reactions Occurring in >25% of Patients Receiving TAGRISSO in ADARA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (n=222)</th>
<th>PLACER (n=443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea†††</td>
<td>23.6</td>
<td>13.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>19.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Abdominal Pain‡</td>
<td>10.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash§§</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Pruritus§</td>
<td>12.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Medullary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>9.5</td>
<td>10.2</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Infection and Infeciton Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>10.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>10.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness*</td>
<td>10.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Metabolism and Nutrient Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Clinical laboratory abnormalities were reported in the majority of patients at baseline. However, clinically meaningful laboratory abnormalities were rarely observed after treatment with TAGRISSO. The incidence of laboratory abnormalities that are known to be associated with administration of EGFR TKIs includes the following:

Table 3. Laboratory Abnormalities Worsening from Baseline in 22% or More of Patients in ADARA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (n=222)</th>
<th>PLACER (n=443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher</td>
<td>All Grades (%)</td>
</tr>
</tbody>
</table>

Table 2 and Table 3 summarize common adverse reactions and laboratory abnormalities which occurred in ADARA.

Table 3. Laboratory Abnormalities Worsening from Baseline in 22% or More of Patients in ADARA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (n=222)</th>
<th>PLACER (n=443)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</thead>
<tbody>
<tr>
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</table>

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<tbody>
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Gastrointestinal Disorders

Oralerta 59 2.2 57 2.5
Stomata 32 0.7 22 0.5
Nausea 14 0 10 0
Constipation 10 0 13 0
Vomiting 11 0.4 11 1.4

Skin Disorders

Rash 59 1.3 17 0.4
Dry skin 78 1.9 38 0.9
Hair loss 10 0 4 0

Metabolism and Nutrition Disorders

Decreased appetite 20 2.5 19 1.8

Respiratory, Thoracic and Mediastinal Disorders

Cough 17 0 15 0.4
Dyspnea 13 0.4 7 0.4

Neurological Disorders

Hypertension 12 0.4 7 0.4

Cardiac Disorders

Prolonged QT interval 10 2 2.2 0.4

Infection and Infestation Disorders

Infectious and parasitic disorders 20 2.5 15 0.4

Musculoskeletal and Connective Tissue Disorders

Cough 17 0 14 0

Nail toxicity¶ 22 0.5 1.5 0
Dry skin§ 23 0 4.4 0

Infectious and parotid disorders 58 1.1 78 7

Skin Disorders

Rash‡ 58 1.1 78 7

Dermatitis acneiform 32 0.7 22 1.1

Drug eruption 46 0.7 48 7

Skin erosion 27 2.2 49 12

Pustule 26 2.2 36 1.5

Hyperkeratosis† 9 1.4 18 1.5

‡ Includes rash, rash generalized, rash erythematous, rash maculo-papular, rash papular, rash purpuric, rash vesicular, urticaria, folliculitis, acne, dermatitis, dermatitis conform, drug eruption, urticaria, vesiculobullous.
§ Includes rash, rash generalized, rash erythematous, rash maculo-papular, rash papular, rash purpuric, rash vesicular, urticaria, folliculitis, acne, dermatitis, dermatitis conform, drug eruption, urticaria, vesiculobullous.
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Clinical relevant adverse reactions in FLAURA in >10% of patients receiving TAGRISSO were alopecia (7%), epistaxis (6%), interstitial lung disease (3%), urticaria (2.2%), palmar-plantar erythrodysesthesia syndrome (1.4%), QTc interval prolongation (1.1%), and decreased appetite (0.4%). QTc interval prolongation represents the incidence of patients who had a QTcF of ≥0.500ms.

Table 7. Laboratory Abnormalities Worsening from Baseline in >10% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>gefitinib or erlotinib (N=131)</th>
<th>All Grades</th>
<th>Any Grade</th>
<th>Grade 3 or Higher</th>
<th>All Grades</th>
<th>Any Grade</th>
<th>Grade 3 or Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
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<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
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<td>Neutropenia</td>
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<td></td>
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<td>Thrombocytopenia</td>
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<td>17</td>
<td>47</td>
<td>13</td>
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<td>Neutropenia</td>
<td>41</td>
<td>3</td>
<td>41</td>
<td>3</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

Effect of Other Drugs on Drug Interactions

Drug Interactions

TAGRISSO and gefitinib or erlotinib were co-administered with a strong CYP3A4 inducer and no apparent drug-drug interaction was observed. Kesugabradine was not developed in patients with end-stage renal disease (CLcr <15 mL/min) as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr <15 mL/min), as estimated by Cockcroft-Gault. There are no clinical data available regarding the use of TAGRISSO in patients with renal impairment.

Table 4. Adverse Reactions Occurring in >10% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>gefitinib or erlotinib (N=131)</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
<th>All Grades (%)</th>
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</tr>
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<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
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<td></td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>43</td>
<td>0</td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>46</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>0</td>
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<tr>
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<td>0.4</td>
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</tr>
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<td>Skin Disorders</td>
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<td></td>
</tr>
<tr>
<td>Rash‡</td>
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<td>1.1</td>
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<td>Hypothyroidia†</td>
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<td>0</td>
<td>31</td>
<td>0</td>
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<td>Hypothyreosis</td>
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<td>0.7</td>
<td>27</td>
<td>0.7</td>
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<tr>
<td>Hyperkalemia</td>
<td>22</td>
<td>1.1</td>
<td>41</td>
<td>1.1</td>
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<tr>
<td>Increased AL</td>
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<td>0.7</td>
<td>28</td>
<td>0.7</td>
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<td>Hyperkalemia</td>
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</table>

**Drug Interactions**

Effect of Other Drugs on Drug Interactions

Drug Interactions

TAGRISSO and gefitinib or erlotinib were co-administered with a strong CYP3A4 inducer and no apparent drug-drug interaction was observed. Kesugabradine was not developed in patients with end-stage renal disease (CLcr <15 mL/min) as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr <15 mL/min), as estimated by Cockcroft-Gault. There are no clinical data available regarding the use of TAGRISSO in patients with renal impairment.
WHEN TREATING CANCERS THAT are considered generally incurable, such as multiple myeloma, one of the paradigms in oncology is to deliver the most effective therapies upfront to maximize the chances of prolonging remission. With the introduction of novel antimyeloma agents, including immunotherapies, that target specific elements of neoplastic plasma cells, we now have the opportunity to explore different combinations of potentially synergistic regimens with the aim of improving survival.1

Nevertheless, challenges remain in determining the optimal regimen for newly diagnosed multiple myeloma (NDMM). These include personalizing treatment decisions based on molecular disease characteristics, overcoming poor prognostic features such as high-risk cytogenetics, and being able to achieve the absence of minimal residual disease (MRD) in a majority of patients.

Fortunately, with the expanding arsenal of agents available to treat patients with multiple myeloma, we are making strides in addressing some of these unmet needs.2

DEVELOPING A COURSE OF TREATMENT
For the purposes of treatment planning, patients with NDMM have been historically separated into those who are eligible or ineligible for high-dose chemotherapy (ie, melphalan) and rescue with autologous stem cell transplant (ASCT), considering that high-dose chemotherapy can prolong survival compared with conventional therapies.3,5 As the eligibility criteria for ASCT has evolved beyond a simple age threshold to assessment of overall fitness,4 more patients are eligible and transplant-related mortality remains low.7

Investigators of the randomized phase 3 IFM/DFCI2009 study (NCT01191060), compared induction with bortezomib (Velcade; V), lenalidomide (Revlimid; R), and dexamethasone—(VRd)—with or without consolidation with ASCT.3 In this study, 700 patients with NDMM with a median age of 59 years were enrolled. Results showed a 30% reduction in risk of progression with the inclusion of transplant; the median progression-free survival (PFS) was 47.3 months vs 35.0 months, respectively (HR, 0.70; P = .0001).8 Although there was no difference in overall survival (OS), with more than 60% of patients alive in both arms at 8 years, 30% vs 20% of patients, respectively, achieved minimal residual disease (MRD) negativity with ASCT (P = .01).

The 3-drug VRd regimen remains a standard upfront regimen for NDMM; however, investigators have examined whether bortezomib or carfilzomib (Kyprolis; K) is a superior proteasome inhibitor (PI). For patients with NDMM with no intention to proceed to ASCT, the phase 3 ENDURANCE study (NCT01863550) compared VRd with KRd,9 and the phase 3 CLARION study (NCT01818752) compared bortezomib, melphalan, and prednisone (VMP) with KMP;10 however, results of both studies failed to show a difference in PFS.

Adverse effects (AEs) were different between each arm, with higher rates of neuropathy associated with bortezomib and more cardiovascular AEs with carfilzomib, suggesting that at the least we can tailor the choice of upfront PI to individual patient morbidities.

Data from the phase 3 FORTE study (NCT02203643) lend support not only to upfront KRd but also to KR maintenance following transplant.2 In this study, 474 patients were randomized to one of 3 arms: KRd with ASCT, KRd without ASCT, or KCd with ASCT (with cyclophosphamide substituted for lenalidomide). Patients in all 3 arms received 4 cycles of induction therapy and 4 cycles of consolidation therapy, followed by a second randomization to either KR or R maintenance.

At a median follow-up of 45 months, patients in the KRd arms had superior outcomes to KCd, with a PFS rate of 78% (KRd + ASCT) vs 66% (KRd) vs 58% (KCd + ASCT). Likewise, at a median follow-up of 31 months from the second randomization, 81% vs 68% of patients were free
from progression when comparing KR vs R maintenance (HR, 0.63; \( P = .026 \)).

**USING TRIPLET REGIMENS AS BUILDING BLOCKS**

In the past few years, 4 monoclonal antibodies (mAbs) have been approved to treat patients with multiple myeloma. Initially these approvals were in the relapsed/refractory setting. More recently, the use of the anti-CD38 mAb daratumumab (Darzalex) has moved to the upfront setting and has been incorporated into guidelines as part of triplet and quadruplet induction regimens (FIGURE).11

Building on the success of a 3-drug regimen for patients with NDMM, results of 3 randomized studies have demonstrated a benefit of adding daratumumab upfront to either VMP (ALCYONE [NCT02195479]12), bortezomib, thalidomide, and prednisone (VIP; Cassiopeia [NCT02541383]13), or VRd (GRIFFIN [NCT02874742]14).

**ALCYONE**

The combination of D-VMP was approved based on findings from the phase 3 ALCYONE study which demonstrated both a PFS and an OS benefit in patients with NDMM who are ineligible for ASCT.12 At a median follow-up of 40 months, the median PFS was 36 months with D-VMP vs 19 months with VMP (HR, 0.42; 95% CI, 0.34-0.51; \( P < .0001 \)). The 36-month OS rate was 78.0% (95% CI, 73.2%-82.0%) vs 67.9% (95% CI, 62.6%-72.6%), favoring D-VMP.

As is common in these studies, the primary AE associated with the addition of daratumumab is myelosuppression. The rate of grade 3 or 4 infections was slightly higher in the daratumumab-containing arm at 22% vs 15%, respectively. However, the discontinuation rate trended lower with the 4-drug regimen.

**GRIFFIN**

For patients with transplant eligible–NDMM, results from both the CASSIOPEIA (D-VTD) and GRIFFIN (D-VRD) studies have shown improvement in depth of response, including the achievement of absence of MRD.13,14

In the randomized phase 2 GRIFFIN study, 207 patients with NDMM were randomized to receive either D-VRd or VRd followed by ASCT. Patients in both arms continued to receive maintenance with either lenalidomide plus daratumumab or lenalidomide alone. There was no second randomization, and participants remained in their respective arms. The primary end point was stringent complete response (sCR).

Results showed that the inclusion of daratumumab did not affect the progression to ASCT, but more individuals needed more agents to facilitate peripheral blood stem cell mobilization. At a median follow-up of 22 months, 99.0% vs 91.8% had achieved a response (OR, 8.75; 95% CI, 1.08-71.01; \( P = .016 \)), with more patients achieving sCR (42.4% vs 32.0%, respectively) and MRD negativity at \( 10^{-5} \) (51% vs 20%) with the addition of daratumumab. Although less than 20% of patients were high risk, there did not appear to be a difference in sCR in the subgroup, and the study is still maturing in terms of PFS and OS analyses.

Clearly the balance of efficacy and toxicity favors the addition of daratumumab to upfront treatment of patients with multiple myeloma. Ongoing studies are evaluating the long-term benefit on OS in those with transplant-eligible NDMM.

**Transplant-Ineligible Patients**

For patients who are transplant-ineligible, investigators of the phase 3 MAIA study (NCT02252172) compared D-Rd with Rd alone in 737 patients with NDMM.15 Recently updated data showed that at a median follow-up of 56 months the 5-year OS rate was 66% vs 53% (HR, 0.68; \( P = .0013 \)) favoring D-Rd. The median time to next treatment was not reached vs 42.4 months, respectively (HR, 0.47; \( P < .0001 \)).16

Although we lack data comparing D-Rd with VRd in patients who are transplant ineligible, data from both MAIA (D-Rd)15 and SWOG S0777 (VRd; NCT00644228)17 demonstrated a survival benefit with 3-drug induction regimens compared with their respective 2-drug control arms. This resulted in a category 1 recommendation from the National Comprehensive Cancer Network for both regimens.11

The phase 3 CEPHEUS (NCT03652064) and PERSEUS (NCT03710603) studies are examining the role of D-Vrd in this population.

**TABLE. Outcomes in the MASTER and MANHATTAN Trials**18-20

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRD-evaluable patients (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD &lt; ( 10^{-5} )</td>
<td>38%</td>
</tr>
<tr>
<td>Overall response</td>
<td>80%</td>
</tr>
<tr>
<td>CR plus MRD &lt; ( 10^{-4} )</td>
<td>73%</td>
</tr>
<tr>
<td>2-year PFS rate</td>
<td>87%</td>
</tr>
<tr>
<td>2-year OS rate</td>
<td>94%</td>
</tr>
</tbody>
</table>

**MANHATTAN**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRD-evaluable patients (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD &lt; ( 10^{-5} )</td>
<td>71%</td>
</tr>
<tr>
<td>Overall response</td>
<td>100%</td>
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<tr>
<td>VGPR/CR</td>
<td>95%</td>
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<tr>
<td>1-year PFS rate</td>
<td>95%</td>
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<tr>
<td>1-year OS rate</td>
<td>100%</td>
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</table>

CR, complete response; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response.

**FUTURE DIRECTIONS**

Ongoing studies are examining the role of mAb-based combination regimens for NDMM. For example, 2 single-arm phase 2 studies, MASTER (NCT03224507)19 and MANHATTAN,19 investigated the combination of D-KRd with or without ASCT, respectively (TABLE).

In the MASTER trial, 81 patients received 4 cycles of D-KRd induction followed by ASCT and MRD-guided consolidation and maintenance R (patients who became MRD-negative entered a treatment-free observation phase). Results of this study showed that an impressive 95% of patients achieved sCR at MRD-based consolidation. In the ongoing phase 2 ADVANCE trial (NCT04268498), investigators are comparing D-KRd vs Rd for patients with NDMM.

In summary, significant progress has been made with novel antimyeloma regimens that include the use of mAbs with or without consolidation with ASCT. Multiple studies are being conducted or conceived to address other important questions, including how to best manage high-risk patients; whether there will be a benefit observed with the addition of novel...
antibodies with induction, such as the anti-BCMA antibody-drug conjugate belantamab mafodotin-blmf (Blenrep), and if there is a role for earlier incorporation of chimeric antigen receptor T cells in the consolidation phase. The 5-year survival rate for multiple myeloma has risen by nearly 10% over the past decade, and is now at a 56%, largely due to novel agents and their combinations. Over the next decade we will likely see the number continue to rise as survival improves.

REFERENCES

Have you seen the data for SARCLISA + Kyprolis® (carfilzomib) and dexamethasone?

Explore the full results of the IKEMA phase 3 trial at sarclisahcp.com
A SINGLE INFUSION OF ciltacabtagene autoleucel (cilta-cel) produced an overall response rate (ORR) of 95% in patients with multiple myeloma who had received a median of 2 prior lines of treatment and who were refractory to lenalidomide (Revlimid), according to updated data from cohort A of the phase 2 CARTITUDE-2 trial (NCT04133636) presented during the 63rd American Society of Hematology Annual Meeting and Exposition.1

At a median follow-up of 14.3 months (range, 3.3-19.0 months), the chimeric antigen receptor (CAR) T-cell therapy elicited responses in 19 of 20 patients (95% CI, 75.1%-99.9%). Of those who responded to treatment, 85% (95% CI, 62.1%-96.8%) achieved a complete response (CR) or better, and 90% (95% CI, 68.3%-98.8%) experienced a very good partial response (VGPR) or better. The median duration of response (DOR) to the treatment had not yet been reached (TABLE 1).

Moreover, of the 13 patients who had samples that were evaluable for minimal residual disease (MRD) at the 10−5 threshold, 92% (95% CI, 64.0%-99.8%) had negative status following treatment.

At a longer median follow-up of 14.3 months (range, 3.3-19.0 months), the chimeric antigen receptor (CAR) T-cell therapy elicited responses in 19 of 20 patients (95% CI, 75.1%-99.9%). Of those who responded to treatment, 85% (95% CI, 62.1%-96.8%) achieved a complete response (CR) or better, and 90% (95% CI, 68.3%-98.8%) experienced a very good partial response (VGPR) or better. The median duration of response (DOR) to the treatment had not yet been reached (TABLE 1).

Limited therapeutic options are available to patients with progressive multiple myeloma who have previously received 1 to 3 lines of therapy and who are lenalidomide-refractory. To address this need, several CAR T-cell therapies are under exploration for potential use in this population. One such product is cilta-cel, which is a therapy that expresses 2 BCMA-targeting, single-domain antibodies that were developed to confer avidity. Results from the phase 1b/2 CARTITUDE-1 trial (NCT03548207) demonstrated that a single cilta-cel infusion was able to produce deep, durable responses in patients with multiple myeloma who had previously received a median of 6 lines of therapy.2

At a median follow-up of 12.4 months (interquartile range, 10.6-15.2 months), 97 patients received the CAR T-cell product. Cilta-cel elicited an ORR of 97% (95% CI, 91.2%-99.4%), with 67% of patients experiencing a stringent CR to treatment. These responses were noted to deepen over time, and the median DOR had not yet been reached (95% CI, 15.9-not estimable [NE]) at a data cutoff of September 1, 2020. At this time, the median progression-free survival (PFS) had also not been reached (95% CI, 16.8-NE).

CARTITUDE-2 STUDY DESIGN AND ADDITIONAL ANALYSIS

For the multicohort CARTITUDE-2 trial, investigators set out to examine the CAR T-cell product in earlier-line settings for patients with multiple myeloma. They are also evaluating whether the product can feasibly be delivered in the outpatient setting.

Cohort A of the trial enrolled patients who had progressive disease following 1 to 3 previous lines of treatment, which included a PI and an immunomodulatory drug. Patients were refractory to lenalidomide and were not previously exposed to a BCMA-targeted agent.1 Study participants underwent a screening period that ranged from 1 to 28 days, followed by apheresis, and then received bridging therapy, if needed. From day -5 to -3, patients were given a lymphodepletion regimen comprising cytarabine at 300 mg/m² plus fludarabine at 30 mg/m². Five to 7 days after lymphodepletion was started, patients were given a single cilta-cel infusion, with a target dose of 0.75 × 10⁸ (range, 0.5 × 10⁸ to 1.0 × 10⁸) CAR-positive viable T cells/kg.
The primary endpoint of the trial was MRD $10^{-5}$ negativity, as evaluated by next-generation sequencing. Key secondary endpoints included ORR, per International Myeloma Working Group response criteria, DOR, time and duration of MRD negativity, as well as incidence and severity of toxicities.

Among the 20 patients enrolled to the cohort, the median age was 60 years (range, 38-75 years), and 65.0% were male. Additionally, 15% had extramedullary disease, 15% had bone marrow plasma cells that were 60% or higher, and 35% had a high-risk cytogenetic profile. Fifteen percent of patients had deletion 17p and 25% had translocation t(14;16). Patients received a median of 2 lines of prior therapy (range, 1-3) and 85% previously underwent autologous stem cell transplantation.

Notably, 65% of patients were triple-class exposed, 40% were triple-class refractory, 20% were penta-drug exposed, and 5% were penta-drug refractory. All participants were refractory to lenalidomide, and 40%, 10%, 35%, and 60% were refractory to bortezomib, carfilzomib, pomalidomide (Pomalyst), and daratumumab (Darzalex), respectively. Ninety-five percent of participants were refractory to the last line of therapy they had received.

Data from the initial analysis of this cohort showed that at a median follow-up of 5.8 months (range, 2.5-9.8 months), cilta-cel was found to elicit an ORR of 95% (95% CI, 75%-100%), with 75% (95% CI, 51%-91%) of patients having achieved a stringent CR or CR. Moreover, 85% (95% CI, 62%-97%) of patients achieved a VGPR or better to the therapy.

At the meeting, Cohen presented updated data from cohort A. Additional data indicated that the median time to first response with cilta-cel was 1.0 months (range, 0.7-3.3 months), and the median time to best response was 2.6 months (range, 0.9-7.9 months).

Moreover, the PFS rate at 6 months was 95% (95% CI, 69.5%-99.3%) with the CAR T-cell product; at 12 months, this rate was 84% (95% CI, 59.1%-94.7%).

Regarding safety, the adverse effects (AEs) experienced by 20% or more of the 20 patients included neutropenia (any grade, 95%; grade 3 or 4, 95%), thrombocytopenia (80%; 35%), anemia (75%; 45%), lymphopenia (65%; 65%), and leukopenia (55%; 55%).

The incidence of initial grade 3 or 4 toxicities that did not recover to at least grade 2 severity by day 60 was 20% for neutropenia, 15% for thrombocytopenia, and 5% for lymphopenia. Additionally, 95% of patients experienced cytokine release syndrome (CRS); 2 of these patients had grade 3 or 4 CRS. The median time to CRS onset in these patients was 7 days (range, 5-9 days) and the median duration was 4 days (range, 2-11 days). Ninety percent of patients had this toxicity resolve at the time of data cutoff. Seventy percent of patients received tocilizumab (Actemra).

Moreover, 3 patients experienced immune effector-cell-associated neurotoxicity syndrome; this was grade 1 in 2 patients and grade 2 in 1 patient. In these patients, the median time to onset was 8 days (range, 7-10 days), and the median duration of the effect was 3 days (range, 1-3 days).

With the implementation of patient management approaches across the CARTITUDE program, the incidence of MNTs was found to decrease, and no MNT cases were reported in this cohort.

Following infusion with the CAR T-cell therapy, 4 patients have died; 2 deaths were caused by disease progression. One patient died of COVID-19, and this was determined to be related to treatment, and 1 patient died because of sepsis that was not determined to be related to cilta-cel.

Follow-up for this cohort is ongoing. In the phase 3 CARTITUDE-4 trial (NCT04181827), investigators are comparing the use of cilta-cel with the combination of pomalidomide, bortezomib, and dexamethasone, and the combination of daratumumab, pomalidomide, and dexamethasone, in patients with relapsed and lenalidomide-refractory multiple myeloma.

## Efficacy

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<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>95.0% (75.1%-99.9%)</td>
</tr>
<tr>
<td>≥CR (95% CI)</td>
<td>85% (62.1%-96.8%)</td>
</tr>
<tr>
<td>≥VGPR (95% CI)</td>
<td>90.0% (68.3%-98.8%)</td>
</tr>
<tr>
<td>Median time to first response, months (range)</td>
<td>1.0 (0.7-3.3)</td>
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<tr>
<td>Median duration of response, months</td>
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<tr>
<td>6-month PFS rate (95% CI)</td>
<td>95.0% (69.5%-99.3%)</td>
</tr>
<tr>
<td>12-month PFS rate (95% CI)</td>
<td>84.0% (59.1%-94.7%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>80%</td>
<td>35%</td>
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<td>Anemia</td>
<td>75%</td>
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<td>Lymphopenia</td>
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<tr>
<td>Leukopenia</td>
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**CAR T-cell–related adverse effects**

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<th>Outcome</th>
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<tbody>
<tr>
<td>CRS</td>
<td>95%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>20%</td>
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CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytotoxic release syndrome; NR, not reached; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response.

## References


Polatuzumab Vedotin Plus R-CHP Improves PFS in Newly Diagnosed DLBCL

by CAROLINE SEYMOUR

THE ADDITION OF POLATUZUMAB vedotin-piq (Polivy) to R-CHP (rituximab [Rituxan], cyclophosphamide, doxorubicin, and prednisone) led to a 27% reduction in the risk of progression or death vs R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with previously untreated, intermediate-risk and high-risk diffuse large B-cell lymphoma (DLBCL). The long-standing standard of care was challenged by investigators in the phase 3 POLARIX study (NCT03274492), the findings of which were presented during a press briefing at the 63rd American Society of Hematology Annual Meeting and Exposition.1

The results also showed that the 24-month progression-free survival rate was 76.7% with the polatuzumab vedotin regimen vs 70.2% with R-CHOP, reflecting an absolute difference of 6.5% (P < .02; FIGURE1-2).

“These results support the use of polatuzumab vedotin plus R-CHP in the initial management of patients with DLBCL,” senior study author Gilles Salles, MD, PhD, a medical oncologist and chief of the Lymphoma Service at Memorial Sloan Kettering Cancer Center, said in a presentation of the data.

R-CHOP has been the frontline standard of care for patients with DLBCL for more than 20 years; however, only 60% to 70% of patients are cured with R-CHOP. Moreover, efforts to improve upon R-CHOP have not yet been successful, leaving a significant unmet need for patients with untreated DLBCL.

On June 10, 2019, the FDA granted accelerated approval to polatuzumab vedotin for use in combination with bendamustine and rituximab (BR) for the treatment of patients with relapsed/refractory DLBCL who have received at least 2 prior therapies.3 The approval of the antibody-drug conjugate was based on results from the phase 1b/2 GO29365 study (NCT02257567), in which 40% of patients who received polatuzumab vedotin plus BR achieved a complete response vs 18% of patients who received BR alone (P = .026).

Moreover, prior findings from a phase 2 study showed that polatuzumab vedotin plus R-CHP was tolerable and elicited encouraging antitumor activity, serving as the basis for the larger, randomized POLARIX study.
The POLARIX trial enrolled patients with previously untreated DLBCL between the ages of 18 and 80 years with an International Prognostic Index (IPI) between 2 and 5 and an ECOG performance score between 0 and 2. Patients were randomized to 1.8 mg/kg of polatuzumab vedotin plus R-CHOP plus a vincristine placebo or R-CHOP plus a polatuzumab vedotin placebo for six 21-day cycles, followed by 375 mg/m² of rituximab in cycles 7 and 8.1,2

Baseline characteristics were well balanced between arms. The median patient age was 65 years (range, 19-80 years) in the polatuzumab vedotin arm vs 66 years (range, 19-80 years) in the R-CHOP arm. Most patients had high-intermediate and high-risk IPI in the polatuzumab vedotin and R-CHOP arms by 62%, as well as double-hit (38% vs 41%) vs triple-hit (8% vs 6%) lymphoma, respectively.

Additional results showed that there was no difference in overall survival between the 2 arms with current follow-up. However, Salles noted that the burden of additional treatment was higher for patients who received R-CHOP.

In terms of safety, any-grade adverse effects (AEs) occurred in 97.9% of patients in the polatuzumab vedotin arm vs 98.4% of patients in the R-CHOP arm; rates of grade 3/4 AEs occurred in 57.7% vs 57.5% of patients, respectively. Grade 5 AEs were reported in 3% of patients on polatuzumab vedotin vs 2.3% of patients on R-CHOP. Serious AEs occurred in 34% of patients on polatuzumab vedotin vs 30.6% of patients on R-CHOP.

AEs leading to discontinuation of any study drug occurred in 6.2% of patients on polatuzumab vedotin vs 6.6% of patients on R-CHOP; discontinuation of polatuzumab vedotin or vincristine occurred in 4.4% vs 5% of patients, respectively.

Dose reduction of any study drug was recorded in 9.2% of patients on polatuzumab vedotin vs 13% of patients on R-CHOP. Notably, the rates of neutropenia and neuropathy were comparable between the treatment arms. “The safety profiles of polatuzumab vedotin plus R-CHOP and R-CHOP were comparable,” Salles said.

REFERENCES
FOR YOUR ADULT PATIENTS WITH PLATINUM-
RESPONSIVE ADVANCED OVARIAN CANCER

IF SHE RESPONDS TO CHEMOTHERAPY

ZEJULA is the only once-daily oral PARP inhibitor maintenance monotherapy approved for all eligible first-line platinum responders with advanced ovarian cancer, regardless of biomarker status

Indication

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

Important Safety Information

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. In PRIMA, the overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≥Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. In PRIMA, Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo, with no reported discontinuations. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose, if necessary.

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

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

**Proven Efficacy in 1L Maintenance Regardless of Biomarker Status\(^1,2\)**

**Overall Population**

(N=733)

- Reduction in the risk of progression or death: 38%

**HRd Population**

(N=373)

- Reduction in the risk of progression or death: 57%

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

**Important Safety Information (continued)**

**Allergic reactions to FD&C Yellow No. 5 (tartrazine):** ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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

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

**Please see Brief Summary on the following pages.**

**References:**


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

Visit ZEJUALHCP.COM to explore the PRIMA data.
BRIEF SUMMARY OF PRESCRIBING INFORMATION
ZEJULA (niraparib) capsules, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.ZEJULA.com.

1 INDICATIONS AND USAGE

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

1.2 Maintenance Treatment of Recurrent Ovarian Cancer
ZEJULA is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

1.3 Treatment of Advanced Ovarian Cancer after 3 or More Chemotherapies
ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
- a deleterious or suspected deleterious BRCA mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy (see Clinical Studies (14.3) of full prescribing information).

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia
Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received monotherapy with ZEJULA in clinical trials. In 1,785 patients treated with ZEJULA in clinical trials, MDS/AML occurred in 15 patients (0.8%).

The duration of therapy with ZEJULA in patients who developed secondary MDS/AML-related AML varied from 0.5 months to 4.9 years. All of these patients had received previous chemotherapy with platinum-based agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

5.2 Bone Marrow Suppression
Hematologic adverse reactions, including thrombocytopenia, anemia, neutropenia, and/or panmyelopaenia have been reported in patients treated with ZEJULA (see Adverse Reactions (6)).

In PRIMA, the overall incidences of >Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 39%, 31%, and 21%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 2%, respectively, of patients. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count:
- >Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 22%, 25%, and 15%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.
- In NOVA, >Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 29%, 25%, and 20%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 3%, 3%, and 2%, respectively, of patients.

In QUADRA, >Grade 3 thrombocytopenia, anemia, and neutropenia were reported in 28%, 27%, and 13%, respectively, of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred in 4%, 2%, and 1%, respectively, of patients.

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

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

In PRIMA, Grade 3 to 4 hypertension occurred in 6% of patients treated with ZEJULA compared with 1% of placebo-treated patients with a median time from first dose to first onset of 43 days (range: 1 to 321 days) and with a median duration of 12 days (range: 1 to 61 days). There were no discontinuations due to hypertension.

In NOVA, Grade 3 to 4 hypertension occurred in 9% of patients treated with ZEJULA compared with 2% of placebo-treated patients with a median time from first dose to first onset of 77 days (range: 4 to 504 days) and with a median duration of 15 days (range: 1 to 86 days). Discontinuation due to hypertension occurred in <1% of patients.

In QUADRA, Grade 3 to 4 hypertension occurred in 5% of patients treated with ZEJULA with a median time from first dose to first onset of 15 days (range: 1 to 316 days) and with a median duration of 7 days (range: 1 to 118 days). Discontinuation due to hypertension occurred in <0.2% of patients.

Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medical manage hypertension with antihypertensive medications and adjustment of the dose of ZEJULA, if necessary (see Dosage and Administration (2.3) and Nonclinical Toxicology (13.2) of full prescribing information).

5.4 Posterior Reversible Encephalopathy Syndrome
Posterior reversible encephalopathy syndrome (PRES) occurred in 0.4% of patients, including intestinal perforation and sepsis, and febrile neutropenia.

Receiving ZEJULA in PRIMAa

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEJULA (%dose-adjusted)</td>
<td>Placebo (%dose-normalized)</td>
<td>ZEJULA (%dose-adjusted)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Constipation</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>41</td>
</tr>
</tbody>
</table>

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) of full prescribing information). ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients. In animal reproductive studies (see Warnings and Precautions (5.3) and Nonclinical Toxicology (13.1) of full prescribing information), no potential to a fetus based on its mechanism of action, animal development, and reproductive toxicology studies were not conducted with niraparib.

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

5.6 Allergic Reactions to FDA Yellow No. 5 (Tartrazine)
ZEJULA capsules contain FDA Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FDA Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- MDS/AML (see Warnings and Precautions (5.1))
- Bone marrow suppression (see Warnings and Precautions (5.2))
- Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
- Posterior reversible encephalopathy syndrome (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 most common adverse reactions of all grades in >10% of 1,314 patients who received ZEJULA in the pooled trials PRIMA, NOVA, and QUADRA trials were nausea (65%), thrombocytopenia (60%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), dyspnea (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer
The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA
Serious adverse reactions occurred in 2% of patients receiving ZEJULA. Serious adverse reactions in ≥2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).

Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation ≥5% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2%) each. Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (53%), and neutropenia (20%).

Table 1 and Table 2 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in all patients treated with ZEJULA in the PRIMA study.

(continued on next page)
Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA. Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months). Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred. Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (3% each) and nausea (2.4%). Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (15%). Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the groups of patients who received ZEJULA.

Table 1: Abnormal Laboratory Findings in >25% of All Patients Receiving ZEJULA in PRIMA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>ZEJULA (n=484) Grades 1-4</th>
<th>Placebo (n=244) Grades 1-4</th>
<th>ZEJULA (n=484) Grades 3-4</th>
<th>Placebo (n=244) Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>87%</td>
<td>66%</td>
<td>29%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>74%</td>
<td>13%</td>
<td>37%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>71%</td>
<td>36%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66%</td>
<td>57%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>66%</td>
<td>25%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>51%</td>
<td>29%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>46%</td>
<td>21%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>40%</td>
<td>23%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>36%</td>
<td>34%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased aspartate amionotransferase</td>
<td>35%</td>
<td>17%</td>
<td>1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Increased alanine amionotransferase</td>
<td>29%</td>
<td>17%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Table 2: Abnormal Laboratory Findings in >10% of Patients Receiving ZEJULA Based on Baseline Weight or Platelet Count in PRIMA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=169) Grades 1-4</th>
<th>Placebo (n=86) Grades 1-4</th>
<th>ZEJULA (n=169) Grades 3-4</th>
<th>Placebo (n=86) Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
<td>54%</td>
<td>5%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>50%</td>
<td>28%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>Neutropeniaα</td>
<td>36%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Leukopeniaα</td>
<td>28%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>53%</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>31%</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>17%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>48%</td>
<td>36%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>21%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Renal and urinary disorders</td>
<td>Acute kidney injury</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>18%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>17%</td>
<td>9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

The following adverse reactions and laboratory abnormalities have been identified in >10% to <15% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, and epistaxis.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of monotherapy with ZEJULA 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in the NOVA trial. Adverse reactions in NOVA led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions in NOVA was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 5: Adverse Reactions Reported in >10% of Patients Receiving ZEJULA in NOVA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZEJULA (n=367) Grades 1-4</th>
<th>Placebo (n=179) Grades 1-4</th>
<th>ZEJULA (n=367) Grades 3-4</th>
<th>Placebo (n=179) Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Thrombocytopenia</td>
<td>61%</td>
<td>5%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>50%</td>
<td>7%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Neutropeniaα</td>
<td>30%</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Leukopeniaα</td>
<td>17%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>74%</td>
<td>35%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>40%</td>
<td>20%</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>34%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Nocicept/diastematism</td>
<td>20%</td>
<td>6%</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>18%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>10%</td>
<td>4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue/asthenia</td>
<td>57%</td>
<td>41%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Psychological disorders</td>
<td>Insomnia</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>17%</td>
<td>9%</td>
<td>5%</td>
</tr>
</tbody>
</table>

(continued on next page)
6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ZEJULA. 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.

Blood and lymphatic system disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Infections and infestations

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td>11</td>
<td>2</td>
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</tbody>
</table>

Metabolism and nutrition disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain</td>
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<td>3</td>
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</tbody>
</table>

Nervous system disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0</td>
</tr>
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Psychiatric disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Diuresis</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Vascular disorders

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 7. Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hemoglobin</td>
<td>83</td>
<td>26</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Increased gamma glutamyl transferase</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8. Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased albumin</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

AST/ALT=Aspartate transaminase/alanine aminotransferase.

*Common Terminology Criteria for Adverse Events version 4.02.

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

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

Table 9. Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

<table>
<thead>
<tr>
<th>Abnormal Laboratory Finding</th>
<th>Grades 1-4</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
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*Common Terminology Criteria for Adverse Events version 4.02.

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Table 10. Abnormal Laboratory Findings in ≥25% of Patients Receiving ZEJULA in QUADRA

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</tr>
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<td>28</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>46</td>
<td>1</td>
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<td>27</td>
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</tr>
</tbody>
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AST/ALT=Aspartate transaminase/alanine aminotransferase.

*Common Terminology Criteria for Adverse Events version 4.02.

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

Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection, and neutropenic sepsis.
**THE ADDITION OF DARATUMUMAB**
(Darzalex) to lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (D-RVd) continued to elicit improved outcomes vs RVd alone in patients with newly diagnosed, transplant-eligible multiple myeloma. The findings from the extended 2-year follow-up analysis of the phase 2 GRIFFIN trial (NCT02874742) were presented during the 63rd American Society of Hematology Annual Meeting and Exposition.1

After a median follow-up of 38.6 months, investigators reported a stringent complete response (sCR) rate of 66.0% for patients who received the quadruple therapy vs 47.4% in patients who received the triplet therapy ($P = .0096$). Investigators also reported that in the intent-to-treat (ITT) population, the minimal residual disease (MRD)-negativity rate, at a threshold of $10^{-5}$, was 64% in patients treated with the quadruple therapy vs 30% in patients treated with the triplet therapy ($P < .0001$).

Although the study was not powered to determine progression-free survival (PFS), at 36 months, the PFS rate trended toward favoring D-RVd compared with RVd alone (88.9% vs 81.2%, respectively). The median PFS was not reached for either group.

"The separation of the PFS rates begins beyond 1 year of maintenance and suggests a benefit of prolonged daratumumab and lenalidomide therapy," said Jacob P. Laubach, MD, MPP, clinical director of the Jerome Lipper Multiple Myeloma Center and senior physician at Dana-Farber Cancer Institute, and an assistant professor of medicine at Harvard Medical School in Boston, Massachusetts, during a presentation of the data.

In the primary analysis of GRIFFIN, D-RVd demonstrated an improved SCR by the end of post-autologous stem cell transplantation consolidation compared with RVd alone (42.4% vs 32.0%, respectively; $P = .0068$).2 Additional follow-up at a median of 27.4 months showed responses were continuing to deepen and favored the daratumumab group vs the RVd group alone (63.6% vs 47.4%; $P = .253$).3 Regarding demographics and clinical characteristics, the treatment arms were well balanced. The median ages reported were 59 years (range, 40-70) in the D-RVd group (n = 104) and 61 years (range, 40-70) for the RVd group (n = 103); 27% of patients were over 65 years of age across both groups. ECOG performance scores, baseline creatinine clearance, and International Staging System (ISS) disease stage were all similar across the treatment groups.

Cytogenetic and revised cytogenetic risk profiles were also similar across groups.

At clinical cutoff, investigators reported that all patients had either completed 2 years of maintenance therapy or discontinued study treatment. "A similar proportion of D-RVd and RVd patients discontinued during the daratumumab/lenalidomide or lenalidomide maintenance period," Laubach said. Reasons for discontinuation during the maintenance period included adverse events, which were balanced between the 2 arms. Laubach noted that more patients who received RVd with lenalidomide maintenance discontinued because of progressive disease.

Over time, response rates for sCR and CR or better were greater for patients in the D-RVd group vs RVd group at all time points, with the deepest responses occurring after 2 years of maintenance therapy. "At last follow-up, rates of complete response or better were 82% for D-RVd vs 61% for RVd," Laubach said.

When a threshold of $10^{-6}$ was used to measure MRD negativity, rates favored D-RVd vs RVd.

**FIGURE. Percent of Patients With MRD Negativity in GRIFFIN**

<table>
<thead>
<tr>
<th></th>
<th>D-RVd (n = 104)</th>
<th>RVd (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>END OF CONSOLIDATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.6%</td>
<td></td>
</tr>
<tr>
<td><strong>AFTER 24 MONTHS OF MAINTENANCE THERAPY</strong></td>
<td>64.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35.6%</td>
<td></td>
</tr>
<tr>
<td><strong>END OF CONSOLIDATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td><strong>AFTER 24 MONTHS OF MAINTENANCE THERAPY</strong></td>
<td>30.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.6%</td>
<td></td>
</tr>
</tbody>
</table>

D-RVd, daratumumab plus lenalidomide, bortezomib, dexamethasone; MRD, minimal residual disease; RVd, lenalidomide, bortezomib, dexamethasone.
in the ITT population—36% vs 15%, respectively (P = .0007). Patients in the D-RVd group also had a favorable CR or better, at 43% vs 22%, respectively (P = .0121).

At both thresholds, MRD-negativity rates were improved for the D-RVd group vs the RVd group at all time points, with the most notable improvements occurring for MRD-negativity rates at the 10⁻⁵ threshold during the first and second years of maintenance therapy.

“In the D-RVd group, 29% of patients who were MRD positive at the end of consolidation became MRD negative at 10⁻⁵ after 2 years of maintenance compared with 12% for RVd, suggesting that adding daratumumab and lenalidomide in maintenance may help achieve MRD negativity,” Laubach said.

Rates of durable MRD negativity lasting over 6 or 12 months were improved in patients who received D-RVd compared with RVd. At over 12 months, D-RVd sustained MRD negativity was 44% compared with 13% for the RVd group.

Regarding safety, higher rates of neutropenia and upper respiratory tract infections were seen in patients treated with D-RVd vs RVd but did not lead to increased rates of treatment discontinuation. Additionally, with the longer follow-up, no new safety concerns were identified. The most common infections, specifically any grade or grade 3/4 infections, and which occurred in over 5% of patients, were similar for both groups.

“These findings support D-RVd as induction, followed by autologous transplant, daratumumab plus RVd post transplant consolidation, and daratumumab and lenalidomide maintenance as an effective strategy for patients with transplant-eligible NDMM [newly diagnosed multiple myeloma],” Laubach said. “These data support the phase 3 PERSEUS study [NCT03710603], which evaluates D-RVd followed by daratumumab and lenalidomide maintenance therapy compared with RVd followed by lenalidomide alone in transplant-eligible NDMM,” Laubach concluded.

REFERENCES

Conference Highlights | ASH 2021

Time-Limited Ublituximab/Umbralisib Plus Ibrutinib Achieves 77% uMRD Rate in CLL

by KRISTI ROSA

**THE ADDITION OF UBLITUXIMAB and umbralisib (Ukoniq; U2) to ibrutinib (Imbruvica) produced deep remissions with favorable tolerability in patients with chronic lymphocytic leukemia (CLL) who previously received ibrutinib and still had detectable minimal residual disease (MRD). The data from a phase 2 trial (NCT04016805) were presented during the 63rd American Society of Hematology Annual Meeting and Exposition.**

Results indicated that 77% of those who went on to receive the triplet combination achieved undetectable minimal residual disease (MRD). Moreover, 4% of patients came off treatment after 24 cycles and continued to have detectable MRD. Nineteen percent of patients remain on therapy with detectable MRD, with the possibility of achieving undetectable levels. The median time to undetectable MRD achievement was 7.4 months (95% CI, 4.6-10.2).

“This is the first non-venetoclax [Venclexta]-containing, MRD-driven, time-limited approach utilizing the combination of a BTK [Bruon tyrosine kinase] inhibitor, a PI3K inhibitor, and an anti-CD20 monoclonal antibody,” Lindsey E. Roeker, MD, lead study author and member of the CLL Program at Memorial Sloan Kettering Cancer Center in New York, New York, said in a presentation on the data. “This add-on approach for patients on continuous ibrutinib resulted in deep remissions that allowed for a tailored, time-limited therapy and sustained treatment-free observation.”

**Time-limited combination strategies have induced high objective response rates that have also proved to be durable in patients with CLL; however, these regimens have also been associated with high rates of toxicities and overtreatment of favorable-risk patients. Additionally, those who receive continuous treatment with single-agent ibrutinib are known to be at risk of cumulative toxicity and acquired resistance.**

This led to the hypothesis that after a period of treatment with ibrutinib, it would be possible to identify a subgroup of patients who had responded to the BTK inhibitor but had detectable MRD and who would derive benefit from a combination approach.

“We asked, could we convert their planned continuous therapy into a time-limited one?” Roeker noted. “In this study, we utilized an add-on approach in which we took patients after an initial period of ibrutinib monotherapy exposure who had detectable MRD, this way preventing overtreatment of those who could have achieved a deeper remission with fewer agents, and added a combination approach until patients achieved undetectable MRD.” At the time that undetectable MRD was achieved, investigators had patients enter a treatment-free observation, in which they would determine what the durability of remission was following treatment discontinuation, Roeker said.

Investigators chose to add the U2 regimen to ibrutinib. An oral, once-daily, inhibitor of PI3Kδ and CK1ε, umbralisib has been shown to have greater retention of T-reg suppressive capacity than agents such as idelalisib (Zydelig) and duvelisib (Copiktra), and to have low rates of immune-mediated toxicity.

The novel, glycoengineered anti-CD20 monoclonal antibody ublituximab has been shown to have enhanced antibody-dependent cellular cytotoxicity vs rituximab (Rituxan).

Data from the phase 3 UNITY-CLL trial (NCT02612311) showed that the U2 combination significantly improved progression-free survival (PFS) over obinutuzumab (Gazyva) plus chlorambucil in patients with CLL. The median PFS was 31.9 months (95% CI, 28.2-35.8).
with U2 vs 17.9 months (95% CI, 16.1-22.6) with the control regimen (HR, 0.546; 95% CI, 0.413-0.720; \( P < .0001 \)).

In November 2021, the FDA scheduled a meeting of the Oncologic Drugs Advisory Committee to review the pending biologics license application/supplemental new drug application for the U2 combination as an option for adult patients with CLL or small lymphocytic lymphoma. The meeting is anticipated to take place in March or April 2022.

The phase 2 trial included patients who had received ibrutinib for at least 6 months. Patients who had detectable MRD could receive the BTK inhibitor in any line.

Patients continued ibrutinib at the previously tolerated dose and then the U2 regimen was added. Umbralisib was administered at a daily dose of 800 mg. Ublituximab was given at 900 mg as a split dose on day 1, and then on days 8 and 15, during cycle 1; then it was given on day 1 of cycles 2 through 6, and on day 1 of every 3 cycles thereafter. Every 3 treatment cycles, MRD was checked.

"For patients who had undetectable MRD, we would then repeat that test 28 days later, and if patients had 2 sequential peripheral blood undetectable MRD results, they would then enter a period of treatment-free observation," Roeker said. "Patients would receive a maximum of 24 cycles of triplet therapy before entering treatment-free observation, and this could occur regardless of MRD status."

If patients experienced progression after being on treatment-free observation for at least 6 months, they were then retreated with U2 plus ibrutinib in accordance with the study protocol. The primary end point of the trial was the rate of undetectable MRD in this population. "We hypothesized that this combination approach would be promising if at least 25 patients were able to convert from detectable to undetectable MRD [status]," Roeker added.

Secondary end points of the trial comprised safety, time to undetectable MRD, PFS, time to progression, overall survival, and response to retreatment.

Twenty-eight patients were evaluable for the safety analysis of the trial, and 27 were evaluable for the efficacy assessment. The median age of patients was 64 years (range, 48-81), 79% were male, and the majority (n = 26) had an ECOG performance status of 0. The median duration of treatment with prior ibrutinib was 21 months (range, 7-67), and the best response to treatment was a partial response.

Moreover, 68% of patients received ibrutinib as their first-line treatment, and 32% received it for relapsed or refractory disease. The number of prior lines of treatment in patients, excluding current ibrutinib, was 1 (range, 1-2), and all patients had previously received chemotherapy. Regarding molecular and cytogenetic features, 67% of patients had unmutated IGHV, 21% had deletion 11q, and 7% had deletion 17p.

"Of those who have been on the triplet therapy, 77% achieved undetectable MRD. Seventeen patients have gone into treatment-free observation," Roeker reported. "We had 1 patient in treatment-free observation who progressed and required subsequent therapy; this was within 6 months of treatment discontinuation, so the patient was not eligible for retreatment protocol."

The [KRI] median time in treatment-free observation was 11 months, and the median time to first undetectable MRD was 6 months, Roeker added. Of the 17 patients who stopped therapy, 53% remain with undetectable MRD.

We have had 1 progression event on this study, but overall, the PFS [data observed with the triplet have] been excellent," Roeker said. When looking at absolute MRD levels over time, Roeker added that these levels were found to decline over time for those on the triplet combination.

Regarding safety, the most common all-grade toxicities reported with treatment included diarrhea (32%), hypertension (18%), anemia (18%), constipation (18%), fatigue (18%), increased alanine transaminase (ALT) or aspartate transaminase (AST) (14%), cough (14%), headache (14%), nausea (14%), COVID-19 (11%), decreased appetite (11%), and decreased weight (11%). The most frequently reported grade 3 or 4 toxicity was diarrhea (4%), followed by hypertension (7%), increased ALT/AST (4%), and COVID-19 (4%).

Two patients discontinued all treatment because of toxicities; 1 did so because of rash and the other because of rash and arthralgia. Both patients had undetectable MRD status at the time of discontinuation. Moreover, 1 patient died because of COVID-19-related complications 103 days after stopping treatment with the U2 regimen.

Investigators continue to enroll patients to the trial. Other cohorts will explore the addition of U2 to agents such as acalabrutinib (Calquence) or venetoclax.

**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.

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 (≥5%) 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.

References:
IMBRUVICA® (ibrutinib) capsules, for oral use

IMBRUVICA in clinical trials

Infections:

Information]. Monitor for signs and symptoms of bleeding. 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 mechanism for the bleeding events is not well understood. Bleeding events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 22% of patients who received IMBRUVICA, respectively. The risk-benefit 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 Warnings and Precautions). Diseases of the respiratory system, including bacterial and viral pneumonitis (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.

Cardiac Arhythmias and Cardiac Failure: Fatal and serious cardiac arhythmias and cardiac failure have occurred with IMBRUVICA therapy. Grade 3 or greater ventricular tachycardias 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 predominantly in patients with cardiac risk factors, high risk infections, and a previous history of cardiac arhythmias (see Warnings and Precautions). At baseline and throughout therapy, monitor patients clinically for cardiac arhythmias and cardiac failure. Obtain an ECG for patients who develop arrhythmias (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arhythmias and cardiac failure appropriately, and if it persists, consider the risks and benefits of IMBRUVICA treatment and follow site-specific modification guidelines (see Dosage and Administration (2.2) in Full Prescribing Information).

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 through treatment with IMBRUVICA as appropriate.

Secondary 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 secondary primary malignancy was non-melanoma skin cancer (8%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA. Assess the risk before therapy 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 Bruton’s D22 and F120 cell rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients in clinical trials. Advise pregnant women of the potential to cause fetal harm. 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).

ADVERSE REACTIONS

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

• Hemorrhage (see Warnings and Precautions)
• Infections (see Warnings and Precautions)
• Cytopenias (see Warnings and Precautions)
• Cardiac Arhythmias and Cardiac Failure (see Warnings and Precautions)
• Hypersensitivity (see Warnings and Precautions)

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

| Body System | Event | Grade 3 (%) | Grade 4 (%)
|-------------|-------|-------------|-------------
| General disorders | Diarrhea | 59 | 4
| | Constipation | 22 | 2
| | Nausea | 20 | 2
| | Stomatitis | 0 | 0
| | Vomiting | 18 | 2
| | Abdominal pain | 14 | 0
| | Dyspepsia | 12 | 0
| Skin and subcutaneous tissue disorders | Bruising | 51 | 2
| | Rash | 25 | 0
| | Petechiae | 16 | 0
| Infections and infestations | Upper respiratory tract infection | 47 | 2
| | Sinusitis | 22 | 6
| | Skin infection | 16 | 6
| | Pneumonia | 12 | 10
| | Urinary tract infection | 12 | 2

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Event</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic disorders</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Diarrhea | 48 | 18
| Nausea | 26 | 18
| Stomatitis* | 17 | 6
| Constipation | 15 | 9
| Vomiting | 14 | 6
| Respiratory, thoracic and mediastinal disorders | Arthralgia | 24 | 0
| | Muscle spasms | 18 | 2
| | Dyspnea | 14 | 0
| | Sinusitis* | 11 | 1
| | Cough | 19 | 0
| | Rash* | 24 | 3
| | Petechiae | 11 | 0
| | Bruising* | 12 | 0
| MucoSklelatal and connective tissue disorders | Muscle spasm | 13 | 8
| | Skin and subcutaneous tissue disorders | All Grades (%) | Grade 3 or Higher (%) |
| | | |
| Diarrhea | 48 | 18
| Nausea | 26 | 18
| Stomatitis* | 17 | 6
| Constipation | 15 | 9
| Vomiting | 14 | 6
| Respiratory, thoracic and mediastinal disorders | Arthralgia | 24 | 0
| | Muscle spasms | 18 | 2
| | Dyspnea | 14 | 0
| | Sinusitis* | 11 | 1
| | Cough | 19 | 0
| | Rash* | 24 | 3
| | Petechiae | 11 | 0
| | Bruising* | 12 | 0

* 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 CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Event</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td></td>
</tr>
</tbody>
</table>
| Diarrhea | 48 | 18
| Nausea | 26 | 18
| Stomatitis* | 17 | 6
| Constipation | 15 | 9
| Vomiting | 14 | 6
| Respiratory, thoracic and mediastinal disorders | Arthralgia | 24 | 0
| | Muscle spasms | 18 | 2
| | Dyspnea | 14 | 0
| | Sinusitis* | 11 | 1
| | Cough | 19 | 0
| | Rash* | 24 | 3
| | Petechiae | 11 | 0
| | Bruising* | 12 | 0

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

Table 4: Adverse Reactions Reported in ≥ 10% of Patients in the IMBRUVICA Treated Arm in Patients with CLL/SLL in RESONATE

<table>
<thead>
<tr>
<th>Body System</th>
<th>Event</th>
<th>All Grades (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
<td></td>
</tr>
</tbody>
</table>
| Diarrhea | 48 | 18
| Nausea | 26 | 18
| Stomatitis* | 17 | 6
| Constipation | 15 | 9
| Vomiting | 14 | 6
| Respiratory, thoracic and mediastinal disorders | Arthralgia | 24 | 0
| | Muscle spasms | 18 | 2
| | Dyspnea | 14 | 0
| | Sinusitis* | 11 | 1
| | Cough | 19 | 0
| | Rash* | 24 | 3
| | Petechiae | 11 | 0
| | Bruising* | 12 | 0

* Based on laboratory measurements per IWCLL criteria and adverse reactions.
The body system and individual ADR terms are sorted in descending frequency order in the IMBRUVICA arm.

* Includes multiple ADR terms
† Includes 3 events of pneumonia with fatal outcome in each arm, and 1 event of pyrexia and upper respiratory tract infection with a fatal outcome in the ofatumumab arm.

** Not used for frequency above 0 and below 0.5%

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 Adverse Reaction</th>
<th>IMBRUVICA</th>
<th>Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment-emergent Grade 4 thrombocytopenia (2% in the IMBRUVICA arm vs 3% in the ofatumumab arm) and neutropenia (8% in the IMBRUVICA arm vs 6% in the ofatumumab arm) occurred in patients.

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA</th>
<th>Ofatumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>51</td>
<td>23</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>36</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 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.

** Not used for frequency above 0 and below 0.5%

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>IMBRUVICA</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Dry eye</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10</td>
<td>12</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 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.

** Not used for frequency above 0 and below 0.5%

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 Adverse Reaction</th>
<th>IMBRUVICA</th>
<th>Placebo + BR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Skin infection*</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>10</td>
<td>2</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 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.

** Not used for frequency above 0 and below 0.5%

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 Adverse Reaction</th>
<th>IMBRUVICA</th>
<th>Chlorambucil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or Higher (%)</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>17</td>
<td>4</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
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>Adverse Reaction</th>
<th>IMBRUVICA + Obinutuzumab (N=113)</th>
<th>Chlorambucil + Obinutuzumab (N=115)</th>
<th>Grade 3 or 4 (N=113)</th>
<th>Grade 3 or 4 (N=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 2</td>
<td>26 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 0</td>
<td>17 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12 0</td>
<td>7 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16 9</td>
<td>14 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 1</td>
<td>16 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13 1</td>
<td>3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 3</td>
<td>7 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 0</td>
<td>3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>11 0</td>
<td>2 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13 1</td>
<td>0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>12 5</td>
<td>0 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 0</td>
<td>4 0</td>
<td></td>
<td></td>
<td></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

1E1912: Adverse reactions described below reflect exposure to IMBRUVICA + rituximab with a median duration of 4.7 months, exposure to FC with a median of 4.7 months in E1912 in patients with 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>Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
<th>Grade 3 or 4 (N=352)</th>
<th>Grade 3 or 4 (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21 2</td>
<td>26 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 0</td>
<td>17 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>12 0</td>
<td>7 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>16 9</td>
<td>14 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 1</td>
<td>16 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin infection*</td>
<td>13 1</td>
<td>3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 3</td>
<td>7 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 0</td>
<td>3 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>11 0</td>
<td>2 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>13 1</td>
<td>0 0</td>
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<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
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<tr>
<td>Arrhythmia</td>
<td>12 5</td>
<td>0 0</td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12 0</td>
<td>4 0</td>
<td></td>
<td></td>
<td></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

1E1912: Adverse reactions described below reflect exposure to IMBRUVICA + rituximab with a median duration of 4.7 months, exposure to FC with a median of 4.7 months in E1912 in patients with previously untreated CLL/SLL who were 70 years or younger.

Table 10: Select Laboratory Abnormalities (≥ 15% Any Grade), New or Worsening from Baseline in Patients Receiving IMBRUVICA (E1912)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMBRUVICA + Rituximab (N=352)</th>
<th>Fludarabine + Cyclophosphamide + Rituximab (N=158)</th>
<th>Grade 3 or 4 (N=352)</th>
<th>Grade 3 or 4 (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>53 30</td>
<td>70 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>43 7</td>
<td>69 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>26 0</td>
<td>51 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38 1</td>
<td>17 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>30 2</td>
<td>15 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>25 3</td>
<td>23 &lt;1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on laboratory measurements per IWCLL criteria

Additional Important Adverse Reactions: Cardiovascular Events: Data on cardiovascular events are based on randomized controlled trials with IMBRUVICA (N=2,115; median treatment duration of 18.1 months for 1,157 patients treated with IMBRUVICA and 5.3 months for 958 patients in the control arm). The incidence of venous or arterial thromboembolic events (venous thrombosis, venous thrombophlebitis, arterial thrombosis, arterial thrombophlebitis, vascular, and cardiac events) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.3% versus 0.0% in patients treated with IMBRUVICA compared to patients in the control arm.

The incidence of atrial flutter and ventricular flutter of any grade was 0.4% versus 1.8% and for Grade 3 or greater was 0.0% versus 0.5% in patients treated with IMBRUVICA compared to patients in the control arm. The incidence of ischemic cerebrovascular events (cerebrovascular accidents, ischemic stroke, transient ischemic attack) of any grade was 1.0% versus 0.4% and of Grade 3 or greater was 0.0% versus 0.2% in patients treated with IMBRUVICA compared to patients in the control arm. In addition, the incidence of cardiac failure of any grade was 1.7% versus 0.5% and for Grade 3 or greater was 1.2% versus 0.3% in patients treated with IMBRUVICA compared to patients in the control arm.

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

- Hepatobiliary disorders: hepatic failure including acute and/or fatal events, hepatic cirrhosis
- Respiratory disorders: interstitial lung disease
- Metabolic and nutrition disorders: tumor lysis syndrome
- Immune system disorders: anaphylactic shock, angioedema, urticaria
- Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome (SJS), erythema multiforme, purpura, neutrophilic dermatoses
- Infections: hepatitis B reactivation
- Nervous system disorders: peripheral neuropathy

Drug Interactions

Effect of CYPIA Inhibitors on Ibrutinib: The coadministration of IMBRUVICA with a strong or moderate CYPIA inhibitor may increase ibrutinib plasma concentrations [see Clinical Pharmacology (12.3) in Full Prescribing Information]. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid concomitant use of other strong CYPIA inhibitors. Interrupt IMBRUVICA if these inhibitors will be used short-term, such as anti-infectives for seven days or less [see Dosage and Administration (2.3) in Full Prescribing Information]. Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain strong or moderate inhibitors of CYPIA.

Effect of CYPIA Inducers on Ibrutinib: The coadministration of IMBRUVICA with strong CYPIA inducers may decrease ibrutinib concentrations. Avoid coadministration with strong CYPIA inducers [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: IMBRUVICA can cause fetal harm based on findings from animal studies. There are no available data on IMBRUVICA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal reproduction studies, administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis at exposures up to 2-30 times the clinical doses of 400-560 mg daily producing embryofetal abnormalities [see Data]. Advise pregnant women of the potential risk to a fetus.

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

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 5 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

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

Lactation: Risk Summary: There is no information regarding the presence of ibrutinib or its metabolites in human milk, the effects on the breastfed 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, Non-clinical 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 to take IMBRUVICA orally once daily according to their physician’s instructions and that the oral dosage (capsules or tablets) should be swallowed whole with a glass of water without opening, breaking or chewing the capsules or cutting, crushing or chewing the tablets approximately the same time each day (see Dosage and Administration (2.1) in Full Prescribing Information).

• Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra doses to make up the missed dose (see Dosage and Administration (2.1) in Full Prescribing Information).

• Advise patients of the common side effects associated with IMBRUVICA (see Adverse Reactions). Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.

• Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products (see Drug Interactions).

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

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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PRC-07287
TARGETING CD166 REPRESENTS A NEW AVENUE OF ATTACK FOR BREAST CANCER

by BRITTANY LOVELY

HIGH EXPRESSION OF ACTIVATED leukocyte cell adhesion molecule, also known as CD166, occurs in approximately 50% of patients with triple-negative breast cancer (TNBC) and up to 80% of patients with estrogen receptor-positive, HER2-negative breast cancer. Investigators have determined, despite not being mutated, amplified, or deleted like other oncogenes and tumor suppressors, the disruption of CD166 has resulted in reductions of tumor progression.

Praluzatamab ravtansine (CX-2009) belongs to a new class of drug conjugates engineered to target tumors that express CD166. The recombinant proteolytically activated antibody prodrugs consist of 4 molecular components: the antibody, a peptide masking the antigen-binding site of the antibody, a protease cleavable linker, and the payload DM4—a potent microtubule inhibitor.

UNTAPPED POTENTIAL

The construct of protease-activatable antibody prodrug enables praluzatamab ravtansine to target high-expression tumor targets without binding to the same target expressed on normal tissue and in circulation (FIGURE 1'). Unlike antibody-drug conjugates, the probody-drug conjugate can effectively target a densely concentrated tumor antigen and have high prevalence in many cancer and tumor types.

The masking peptide blocks antigen binding, allowing the prodrug conjugate to interact with healthy tissue without releasing the cytotoxic payload. The substrate links remain stable in vivo in circulation until interaction with protease, which have dysregulated activity in cancer tissue. Once the protease cleaves the masking peptide, the parental antibody is activated.

SUMMARY OF PHASE 1 CLINICAL ACTIVITY

Praluzatamab ravtansine was validated in a dose-finding safety analysis from the phase 1/2 PROCLAIM-CX-2009 trial (NCT03149549) in which a total of 96 patients, 42 of whom had breast cancer and received doses ranging from 4 to 10 mg/kg. CD166 expression was evaluated by immunohistochemistry and was defined as 3+ in at least 50% of tumor cells. In total, 77 patients had high expression, 13 had low expression, and 6 were reported as unknown.

The median number of prior treatments for the patient population was 5 (range, 1-9). Patients received a median of 2 doses (range, 1-15) of praluzatamab ravtansine. The maximum tolerated dose was not reached. However, with dose-limiting toxicities and treatment-related adverse effects, this resulted in the conclusion that the recommended phase 2 dose be 7 mg/kg.

Partial responses were reported among 8 patients, and 2 of those were confirmed in patients with hormone receptor-positive, HER2-negative breast cancer. Further, stable disease was observed in 21 patients, 5 of whom had stable disease of at least 3 months.

Specific to the cohort of patients with breast cancer, 11 patients had TNBC and 25 had hormone receptor-positive, HER2-negative disease. Prevalence of CD166 was high in most patients (6 and 23 patients, respectively), and the median number of prior treatments was 7 (range, 3-16). Prior therapies among the TNBC and hormone receptor-positive, HER2-negative populations included platinum (9 and 4 patients, respectively), microtubule inhibitors (11 and 24), and PD-L1/PD-1 inhibitors (4 and 1). No patients with TNBC received prior CDK4/6 inhibitors compared with 16 patients with hormone receptor-positive, HER2-negative disease.

Response assessments were available for 8 patients with TNBC and 18 patients with hormone receptor-positive, HER2-negative disease. Unconfirmed partial responses were reported for 3 patients with TNBC. Investigators reported stable disease in 9 patients, 8 of whom had hormone receptor-positive, HER2-negative breast cancer. The clinical benefit rate—defined as complete response, partial response, or stable disease—was 39% at 16 weeks and 35% at 24 weeks.

At the recommended phase 2 dose, no dose-limited toxicities were reported with praluzatamab ravtansine. Toxicities related specifically to the DM4 payload included ocular, neuropathic, and hepatic, which were higher in patients who received doses greater than 8 mg/kg.

One instance of grade 3 or higher ocular toxicity was reported with praluzatamab ravtansine at 5 mg/kg compared with 3, 3, 2, and 1 instance reported for 8 mg/kg, 9 mg/kg, and 10 mg/kg, respectively. Two instances of grade 3 or higher ocular toxicity were reported when praluzatamab ravtansine was administered at 6 mg/kg every 2 weeks.

MOVING FORWARD WITH MONOTHERAPY AND COMBINATION REGIMENS

Investigators have initiated a phase 2 prospective, open-label CTMX-2009-002 trial (NCT04596150) of praluzatamab ravtansine, which will enroll patients with 1 of 3 parallel arms (FIGURE 2). Arm A will include up to...
Clinical Trial In Focus

40 patients with hormone receptor-positive, HER2-negative breast cancer to receive praluzatamab ravtansine monotherapy. Arm B will enroll 40 patients with TNBC who will receive praluzatamab ravtansine monotherapy. Arm C will include 40 patients with TNBC who will receive praluzatamab ravtansine in combination with the monoclonal antibody, CX-072. All patients will receive CX-2009 at the recommended dose of 7 mg/kg, and those in the combination arm will receive CX-072 at 1200 mg. All regimens are administered once every 3 weeks.2,9

Per RECIST 1.1 criteria, investigators will assess tumors every 6 weeks for the first 48 weeks on treatment and every 12 weeks thereafter.2 The primary efficacy measure is objective response rate. Additional outcome measures include investigator-assessed progression-free survival, duration of response, overall survival, and clinical benefit rate at 16 and 24 weeks.2

RECRUTMENT FOR CTMX-2009-002 IS UNDERWAY

To be eligible for enrollment, patients must have a measurable disease, an ECOG performance status of 0 or 1, and have adequate hematologic, renal, and hepatic function. In arms B and C, patients must have received 1 to 3 prior lines of therapy for inoperable, locally advanced, metastatic TNBC. They may also have fresh tumor tissue with high CD166 expression per immunohistochemistry. Those in arm A may have received up to 2 prior treatments with cytotoxic chemotherapy. In the combination arm, patients must be PD-L1 positive by an FDA-approved test.2,9

Patients with a prior malignancy within the past 2 years are not eligible unless the patient is considered at low risk for recurrence, or the localized cancer is not related to the current cancer being treated in the study. Because of the risk of ocular toxicities with praluzatamab ravtansine, investigators are also prohibiting the enrollment of patients with active or chronic corneal disorders.3

In terms of central nervous system metastases, if a patient presents with metastases that measure 1 cm or less, are asymptomatic, and require treatment, investigators may assess individuals for eligibility. Investigators have added additional exclusion criteria for the combination arm, including history of or current autoimmune disease, myocardiitis, or history of intolerance to prior immune checkpoint inhibitor therapy. Those who require immunosuppressive therapy, including the use of chronic systemic steroids within 14 days of initiation of trial therapy, are not permitted. However, patients who require brief treatment with steroids may be evaluated on an individual basis.2,9

The trial is open to enrollment. ■

REFERENCES

FIGURE 2. CX-2009 Monotherapy and in Combination With CX-072 in Advanced Breast Cancer (NCT04596150)†

ELIGIBILITY CRITERIA

Arm A
• Inoperable, locally advanced or metastatic HR-positive/HER2-negative breast cancer
• ≤ 2 prior cytotoxic chemotherapy in the inoperable, locally advanced, or metastatic setting

Arm B and arm C
• Inoperable, locally advanced or metastatic TNBC
• Archival or fresh tumor tissue must have high CD166 expression per immunohistochemistry.
• ≥ 3 prior lines of therapy for inoperable, locally advanced, or metastatic TNBC

Arm C only
• Patients must be PD-L1-positive by an FDA-approved test
• If checkpoint inhibitors therapy was the most recent treatment given prior to enrollment into this study, the patient must not have progressed within 120 days of the first dose of the therapy
• Measurable disease per RECIST 1.1
• ≥ 18 years old
• ECOG performance status of 0 or 1

* CB, clinical benefit rate; DOR, duration of response; HR, hormone receptor; ORR, objective response rate; OS, overall survival; TNBC, triple-negative breast cancer.

PRIMAR Outcome
• ORR
SECONDARY OUTCOMES
• DOR
• OS
• CBR at 16 weeks and 24 weeks

Vol. 23 | No. 1 | JANUARY 2022 41
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.

Learn more at BLENREPHCP.com
**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 14% of patients. Changes in 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. 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 18%, and Grade 4 in 17%. 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 1 in 1%, Grade 2 in 3%, and Grade 4 in 1%. The median time to onset of the first infusion-related event was 3 days. Infusion-related reactions occurred in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 infusion-related reactions 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.

**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.

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. 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 (21%) 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%).

**USE IN SPECIFIC POPULATIONS**

**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.

**Renal or Hepatic Impairment:** The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis. The recommended dosage has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and any AST).

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.
BLENREP
(belantamab mafodot-blmf)
for injection, for intravenous use

The following is a brief summary only; see full Prescribing Information for complete product 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 [see Warnings and Precautions (5.1)].

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 [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a REMS called the BLENREP REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE
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 [see Clinical Studies (14) of full Prescribing Information] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
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% of 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% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had 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 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. Withhold 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)].

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 13%, 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 resolved as 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 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 [see Use in Specific Populations (8.1, 1, 2, 3)].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- 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) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in 3% of patients included pneumonia (1%), 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%).

(continued on next page)
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 pain (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.

**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, 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-blmf, 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-blmf 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 defects, 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-blmf. 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.

(continued on next page)
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 serum creatinine >2.0 mg/dL or dialysis; serum creatinine >1.5 mg/dL in patients on hemodialysis or peritoneal 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

Advise 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)].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see Warnings and Precautions (5.2)]. Inform the patient of the following notable requirements:

• Patients must complete the enrollment form with their provider.

• Patients must comply with ongoing monitoring for eye exams [see Warnings and Precautions (5.1)].

Thrombocytopenia

• Advise patients to inform their healthcare provider if they develop signs or symptoms of bleeding [see Warnings and Precautions (5.3)].

Infusion-Related Reactions

• Advise patients to immediately report any signs and symptoms of infusion-related reactions to their healthcare provider [see Warnings and Precautions (5.4)].

Embryo-Fetal Toxicity

• Advise pregnant 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 (5.5), Use in Specific Populations (8.1, 8.3)].

• Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)].

• 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 Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

• Advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose [see Use in Specific Populations (8.2)].

Infertility

• Advise males and females of reproductive potential that BLENREP may impair fertility [see Use in Specific Populations (8.3)].

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Surgical Resectability Remains Crucial in Determining Treatment Strategy in Liver-Only Metastatic CRC

by MAGGIE TIBBITT

EARLY IDENTIFICATION OF PATIENTS with liver-only metastatic colorectal cancer (CRC) who are eligible for resection is crucial to determining their course of treatment and what role modalities, such as chemotherapy, will play in their treatment strategy, according to Patrick Boland, MD. “We need to consider patients who are initially resectable vs patients who are not initially resectable differently, because the goals are different,” Boland said. “For patients who are initially resectable, the goal of chemotherapy is to reduce the risk of recurrence, [or possibly] to biologically select patients who should undergo surgery. For patients who are not resectable upfront, the goal is to shrink the tumor as much as we can to enable surgery. [This] leads us to think about more aggressive treatments.”

In an interview with OncologyLive®, Boland, a medical oncologist and member of the gastrointestinal oncology team at RWJBarnabas Health and Rutgers Cancer Institute of New Jersey in New Brunswick, discussed the evolution of treatment for patients with liver-only metastatic CRC and the different treatment options for those whose disease is initially resectable vs not initially resectable.

Please provide a brief overview of the treatment options available for patients with liver-only metastatic CRC.

BOLAND: There is a debate [about] what chemotherapy adds [to treatment]. Right now, it is the standard. When [considering] patients as a whole, we [must] think about those who are initially resectable up front, or those who are not resectable but are convertible with chemotherapy, or at least [who are at] risk for positive margins. For patients with resectable disease, the EPOCH trial [NCT01483027] and the phase 2/3 JCOG0603 trial both [demonstrated] a decrease in rates of recurrence with the use of perioperative 5-fluorouracil, leucovorin, and oxaliplatin [FOLFOX]. However, [neither trial] demonstrated a survival benefit. We can look at that a few different ways, but one of the major goals of giving chemotherapy is to increase the rate of curing patients and decrease the risk of recurrence. The gold standard is survival, and that is what we would love to show. The fact that patients can go on to be salvaged with other therapies proves the bar is perhaps too high for any of these studies to show individually.

Right now, perioperative chemotherapy remains a standard, with FOLFOX or capecitabine plus oxaliplatin [CAPOX] being the [usual choice]. There have been other studies looking at adding targeted drugs in resectable disease, but to date, they have failed to show any improvement. For instance, cetuximab [Erbitux] failed to show improvement, so we do not recommend that in resectable disease upfront.

On the other hand, with disease that is not resectable initially, the options for therapies keep expanding. We have seen an increased use of triplet chemotherapy, such as FOLFOXIRI [folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin] or FOLFIRINOX [5-fluorouracil, irinotecan, and oxaliplatin], which gives very high response rates. We also have some data that adding bevacizumab [Avastin] to FOLFOX improves response rates and [might] protect the liver. The good news is that as we learn how to better use therapies, we have more options. The tricky part is figuring out how to use the right amount at the right time.

Please highlight some of the trials investigating triplet chemotherapy options.

In the phase 2 OLIVIA trial [NCT00778102], patients received FOLFOXIRI and bevacizumab and we saw that there is a higher rate of R0 resection with the use of triplet chemotherapy vs doublet chemotherapy [TABLE].1 We do not know [whether] that translates to improved long-term outcomes yet. However, if you believe getting patients to surgery gives them the best long-term odds, then certainly for patients that are not resectable initially, and who are fit enough to receive triplet chemotherapy, this represents a feasible option.

There are also Japanese data looking at which biologics should be used if we are giving triplet therapy to patients who are RAS wild type. Is bevacizumab better, or is cetuximab better? [Based on] the DEEPER study (JACCRO CC-13, UMIN000018217) that was presented at the 2021 American Society of Clinical Oncology Annual Meeting, we see both have similar response rates, which [might be] surprising. We get a bit of a deeper response with the anti-EGFR drugs, but the number of patients who undergo high-quality resections did not differ. There is not

**TABLE. Outcomes in the OLIVIA Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bevacizumab + FOLFOXIRI (n = 41)</th>
<th>Bevacizumab + mFOLFOX-6* (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall resection rate (95% CI)</td>
<td>61% (45%-76%)</td>
<td>49% (32%-63%)</td>
</tr>
<tr>
<td>R0 resection rate</td>
<td>49%</td>
<td>23%</td>
</tr>
<tr>
<td>Overall tumor response rate (95% CI)</td>
<td>81% (65%-91%)</td>
<td>62% (45%-77%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>18.6 (12.9-22.3)</td>
<td>11.5 (9.6-13.6)</td>
</tr>
</tbody>
</table>

FOLFOXIRI, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; mFOLFOX-6, modified oxaliplatin, folinic acid, 5-fluorouracil, PFS, progression-free survival.

*Modified regimen defined as oxaliplatin 85 mg/m², folinic acid 400 mg/m², 5-fluorouracil 400 mg/m² (bolus) then 2400 mg/m² (46-hour infusion).
necessarily a preferred [agent] in that space. I tend to lean toward bevacizumab, but we can look at this on a case-by-case basis, based on how much response a patient needs and who the patient is.

Q What patient characteristics help guide your treatment decisions?

The first thing we look at is how much disease there is in the liver, and then any other risk factors. Does the patient have synchronous or metachronous presentation? Do we know anything about mutational status or poor prognosticators, such as whether the patient is RAS mutated or BRAF mutated? Do we know anything about the primary [tumor], and is it intact? Was it resected or node positive?

Bilobar disease, metastases, and mutations are all bad prognosticators, and patients with these characteristics are more likely to be given chemotherapy up front, even if they are resectable. We do not know [whether] that is the best way to get long-term outcomes, but in general, our practice commonly gives perioperative chemotherapy upfront.

We try to limit [perioperative chemotherapy] as much as possible. The aim is to give no more than 2 to 3 months if the patient is resectable at that time. [We give patients] frequent scans every 6 to 8 weeks to reassess. This always requires an upfront visit with a hepatobiliary surgeon, which needs to be on the radar when patients have liver-only metastases. Even if you [suspect] the [patient] is not resectable, it is worth a discussion whether portal vein embolization or some other out-of-the-box techniques can be employed.

Q Are there any other areas that have been pivotal to expanding the treatment options for these patients?

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Infigratinib Shows Promising Early Activity in FGFR2-Altered Cholangiocarcinoma

by COURTNEY MARABELLA

THE FGFR INHIBITOR INFIGRATINIB
(Truseltiq) demonstrated promising clinical activity and a manageable safety profile in previously treated patients with locally advanced or metastatic cholangiocarcinoma whose tumors harbor FGFR2 gene fusions or rearrangements. Investigators in a phase 2 trial (NCT02150967) believe these data published in *The Lancet Gastroenterology and Hepatology* could represent a new tool to treat this disease.1

Results showed that at a median follow up of 10.6 months (range, 6.2-15.6), the blinded independent central review (BICR) assessed objective response rate (ORR) with infigratinib was 23.1% (95% CI 15.6%-32.2%). These findings included 1 complete response (CR; 1%) and 24 partial responses (PRs; 22%).

“Infigratinib, administered as a second-line or later-line treatment, represents a potential new therapeutic option for patients with cholangiocarcinoma and FGFR2 fusions or rearrangements,” study authors wrote. Based on these data the agent received an accelerated approval from the FDA in May 2021.

For patients with locally advanced or metastatic cholangiocarcinoma, the standard-of-care first-line treatment is gemcitabine plus cisplatin chemotherapy. Second-line treatment options include FOLFOX and gemcitabine- or fluorouracil-based combinations, although evidence is lacking for specific recommendations in this setting. Moreover, investigators have identified molecular drivers implicated in the development of specific cholangiocarcinoma subtypes, such as FGFR alterations, and second-line chemotherapy regimens have shown limited efficacy in patients with these alterations.

Previous phase 1 and 2 trials examining FGFR inhibitors have shown single-agent CRs and PRs in patients with FGFR2-altered cholangiocarcinoma, as well as the development of treatment resistance through mutations in FGFR2. This further supports utilizing FGFR2 fusions as a therapeutic target for molecularly selected patients.

The FDA has issued accelerated approvals for the FGFR inhibitors erdafitinib (Balversa) and pemigatinib (Pemazyre) have received by the FDA for this patient population. The agency granted a breakthrough therapy designation to a third FGFR inhibitor, futibatinib, in April 2021. However, investigators want to develop more agents to

Liver Metastases in CRC

- Treatment strategies aimed at allowing hepatic resection offer better 5-year survival rates than palliative treatment alone.
- Clarification of resectability status is a priority in the treatment of patient with colorectal cancer (CRC) with liver metastases.
- Despite chemotherapy demonstrating the ability to downsize metastases, there is no standard approach to treat patients with liver-only metastases.
- Guidelines suggest doublet chemotherapy plus targeted agents, such as bevacizumab, up front.

REFERENCE
address the heterogeneity of FGFR alterations and the emergence of resistance mechanisms.

Infigratinib is a potent, selective ATP-competitive inhibitor of FGFR, with single-digit nanomolar inhibitory concentration values. Additionally, the agent has shown single-agent activity and a manageable safety profile against tumors with FGFR alterations in early clinical studies. As such, investigators sought to evaluate the antitumor activity of infigratinib in patients with locally advanced or metastatic cholangiocarcinoma, whose tumors harbor FGFR2 alterations, and who had received previous gemcitabine-based chemotherapy.

Investigators are conducting the 3-arm, phase 2, open-label, multicenter trial at 18 academic centers and hospitals in the United States, Belgium, Spain, Germany, Singapore, Taiwan, and Thailand. Cohort 1 is comprised of patients with FGFR2 fusions or rearrangements who have not received previous selective FGFR inhibitors. Cohort 2 will comprise patients with FGFR1 mutations and fusions or rearrangements, FGFR3 mutations and fusions or rearrangements, or FGFR2 mutations, who have not previously received an FGFR inhibitor. Finally, Cohort 3 will recruit patients with FGFR2 fusions or rearrangements who had received previous treatment with an FGFR inhibitor other than infigratinib.

Adults with histologically or cytologically confirmed cholangiocarcinoma with FGFR2 fusions or rearrangements are eligible for Cohort 1. Eligible patients were also required to have received at least 1 previous gemcitabine-based regimen for advanced or metastatic disease, as well as documented progression following that previous regimen or discontinuation from the previous regimen because of toxicity, an ECOG performance status of 1 or less, and measurable disease.

Patients were assigned to 125 mg once-daily oral infigratinib for 21 consecutive days in 28-day cycles until disease progression, intolerance, withdrawal of consent, or death. Patients were allowed dose modifications and/or treatment interruptions of up to 14 days for the management of adverse effects (AEs).

The primary end point of the study was BICR-assessed ORR. Secondary end points included investigator-assessed ORR, BICR-assessed and investigator-assessed best overall response, BICR-assessed and investigator-assessed disease control rate (DCR), time to response (TTR), BICR-assessed and investigator-assessed progression-free survival (PFS), overall survival (OS), safety, and tolerability.

Among the 108 patients enrolled on Cohort 1 of the study, the median age was 53 years old (range, 44-64), and a majority were female (62%), White (72%), and located in North America (71%). Fifty-seven percent of patients had an ECOG performance status of 1, and 99% had stage IV disease. Additionally, 69% of patients had extrahepatic metastasis in the lungs, 57% in the lymph nodes, 26% in the bone, 15% in the peritoneum or ascites, and 33% in other locations. Furthermore, 63% had 2 or more metastatic sites, and 46% had received 1 or more lines of prior treatment.

The median TTR was 3.6 months (range, 1.8-3.8) and the median duration of response (DOR) was 5.0 months (range, 3.7-9.3). DCR was 84.3% (95% CI, 76.0%-90.6%). The investigator-assessed ORR was 36.0% (95% CI, 22.1%-49.4%) and the median investigator-assessed DOR was 6.0 months (range, 4.9-9.2). The discordance rate of BICR-assessed vs investigator-assessed confirmed responses was 20.4%. At the time of data cutoff, the median PFS was 7.3 months (95% CI, 5.6-7.6) and the median OS was 12.2 months (95% CI, 10.7-14.9). Furthermore, the median duration of treatment with infigratinib was 5.5 months (range, 3.5-8.7).

In terms of safety, the most common treatment-emergent AEs of any grade were hyperphosphatemia (77%), stomatitis (55%), fatigue (40%), alopecia (38%), and dry eye (34%; Table). The median time to first onset of hyperphosphatemia was 8 days (range, 8-15), and no patients discontinued treatment because of hyperphosphatemia. Overall, 69% of patients experienced AEs leading to dose reduction and 64% had AEs requiring dose interruption.

“Results from cohorts 2 and 3 of this study will provide further clarification regarding the role of infigratinib in patients with cholangiocarcinoma and FGFR1 and FGFR3 fusions and rearrangements, FGFR1, FGFR2, and FGFR3 mutations, and in patients previously treated with FGFR inhibitors other than infigratinib,” the study authors concluded.

TABLE. Treatment-Emergent Adverse Events in a Phase 2 Trial (NCT02150967)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Infigratinib (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>28%</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>77%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>55%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>34%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>29%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>13%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>12%</td>
</tr>
</tbody>
</table>

REFERENCE

UKONIQ is indicated for the treatment of adult patients with:
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least 1 prior anti-CD20-based regimen
- Relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy

**THE POWER IS WITH U**

**2 PATHWAYS, 1 FOCUS.**

**UKONIQ:** THE FIRST AND ONLY TARGETED KINASE INHIBITOR OF PI3K-DELTA AND CK1-EPISILON

UKONIQ was evaluated in an open-label, multi-cohort, single-arm study in 69 patients with MZL who received at least 1 prior therapy (including an anti-CD20 regimen) and 117 patients with FL who received at least 2 prior systemic therapies (including an anti-CD20 monoclonal antibody and an alkylating agent).

Efficacy was based on ORR as assessed by an IRC using criteria adopted from the IWG for malignant lymphoma.

- **MZL ORR:** 49% (n=34/69; 95% CI, 37.0–61.6); CR=16%, n=11/69; PR=33%, n=23/69
- **MZL mDOR:** NR (95% CI, 9.3–NE; range, 0.0–21.8*)
- **FL ORR:** 43% (n=50/117; 95% CI, 33.6–52.2); CR=3.4%, n=4/117; PR=39%, n=46/117
- **FL mDOR:** 11.1 months (95% CI, 8.3–16.4; range, 0.0–20.9*)

The pooled safety data reflect 221 patients with MZL and FL who received UKONIQ 800 mg orally once daily in 3 single-arm, open-label trials and 1 open-label extension trial.

*Denotes censored observation.

**IMPORTANT SAFETY INFORMATION**

**Infections:** Serious, including fatal, infections occurred in patients treated with UKONIQ. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. Provide prophylaxis for Pneumocystis jirovecii pneumonia (PJP) and consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation. Monitor for any new or worsening signs and symptoms of infection, including suspected PJP or CMV, during treatment with UKONIQ. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

**Neutropenia:** Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil count <1 x 10^9/L (Grade 3–4) neutropenia during treatment with UKONIQ. Consider supportive care as appropriate.

**Diarrhea or Non-Infectious Colitis:** Serious, including fatal, diarrhea or colitis occurred in patients treated with UKONIQ. Grade 3 or higher diarrhea or colitis occurred in 22% of 335 patients and Grade 4 occurred in 9%. For patients with severe diarrhea (Grade 3, i.e., >6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or perineal signs, withhold UKONIQ until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis.

**Hepatotoxicity:** Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients. Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ.

**Severe Cutaneous Reactions:** Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with
UKONIQ ADVERSE REACTIONS IN ≥10% OF PATIENTS (N=221) FROM A POOLED SAFETY POPULATION1,2

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>14</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>27</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>&lt;1</td>
<td>0</td>
</tr>
</tbody>
</table>

ADDITIONAL CLINICALLY RELEVANT ADVERSE EVENTS IN PATIENTS WHO RECEIVED UKONIQ1,2

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis</td>
<td>2.4</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>32</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>33</td>
<td>5.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade. Provide supportive care as appropriate.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5: UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons, frequently in patients who also have aspirin hypersensitivity.

Embryo-fetal Toxicity: Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose.

Serious adverse reactions occurred in 18% of 221 patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients.

Lactation: Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for at least one month after the last dose.

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

2. TG Therapeutics, Inc. data on file.
5.5. Severe Cutaneous Reactions
Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular) [see Adverse Reactions (6.1)]. The median time to onset of Grade 3 or higher cutaneous reactions was 2.9 months (range: 2 days to 6.4 months). Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsen, or recur. Dose reductions of UKONIQ may be considered during treatment with UKONIQ for serious cutaneous reactions.

5.6. Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5
UKONIQ contains FD&C Yellow No. 5 (tartarazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartarazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

5.7. Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, UKONIQ caused fetal abnormalities when administered to pregnant mice during the period of organogenesis caused adverse developmental outcomes including embryo-fetal mortality and fetal malformations at maternal exposures equal or barely attainable to those in patients at the recommended dose of 800 mg. 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 and for one month after the last dose [see Use in Specific Populations (8.1, 8.3)].

6. ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Infections [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Diarrhea and Non-Infectious Colitis [see Warnings and Precautions (5.3)]
- Hematologic [see Warnings and Precautions (5.4)]
- Severe Cutaneous Reactions [see Warnings and Precautions (5.5)]

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 compared to rates in the clinical trials of another drug and may not reflect the rates observed in the general population. The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to UKONIQ as monotherapy at a dosage of 800 mg orally once daily in 335 adults with hematologic malignancies in studies IGR-102-01, IGR-102-02, IGR-050, and IGR-501. Among these 335 patients who received UKONIQ, 52% were exposed for 6 months or longer and 30% were exposed for greater than one year.

6.2. Neutropenia
Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9% [see Adverse Reactions (6.1)]. The median time to onset of Grade 3 or neutropenia was 45 days. Median time to recovery of neutrophils was at least 4 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts <1 x 10^9/L (Grade 4). Consider supportive care as appropriate. Withhold UKONIQ, reduce dose, or discontinue UKONIQ, depending on the severity and persistence of neutropenia [see Dosage and Administration (2.2)].

6.3. Diarrhea or Non-infectious Colitis
Serious diarrhea or non-infectious colitis occurred in patients treated with UKONIQ. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9% [see Adverse Reactions (6.1)]. The median time to onset for any grade diarrhea or colitis was 1 month (range: 1 to 23 months), with 75% of cases occurring by 2.9 months. For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) or abdominal pain, stool with mucus or blood, change in bowel habits, or perianal signs, withhold UKONIQ until resolved and provide appropriate supportive care with antidiarrheals or enteric acting stools as appropriate. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis [see Dosage and Administration (2.3)].

6.4. Hepatotoxicity
Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients [see Adverse Reactions (6.1)]. The median time to onset for Grade 3 or higher transaminase elevations was 2.2 months (range: 5 days to 4.7 months). Monitor hepatic function at baseline and during treatment with UKONIQ. For ALAT greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALAT elevation greater than 20 times ULN, discontinue UKONIQ [see Dosage and Administration (2.3)].

5.4.2 Renal Function
Serum creatinine increased in patients treated with UKONIQ. Grade 3 and 4 increases in serum creatinine occurred in 1% and <1%, respectively, in 335 patients [see Adverse Reactions (6.1)]. The median time to onset for Grade 3 or higher increases in serum creatinine was 1.9 months (range: 5 days to 4.7 months). Monitor creatinine at baseline and during treatment with UKONIQ. For serum creatinine >3 times ULN, withhold UKONIQ until return to <3 times ULN, then resume at a reduced dose. For serum creatinine >5 times ULN, discontinue UKONIQ [see Dosage and Administration (2.3)].

5.5.2 Transaminase Elevation
Severe transaminase elevations occurred in patients treated with UKONIQ. Grade 3 transaminase elevations occurred in 2% of 335 patients and included transaminase elevation (7%), neutropenia (5%), vomiting (5%), and upper respiratory tract infection (5%). The most common (≥15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diaphoresis, fatigue, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash.

Table 3: Adverse Reactions Reported (≥10%) in Patients With Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

<table>
<thead>
<tr>
<th>UKONIQ N=221</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abdominal pain includes Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort

*Fatigue includes Fatigue, asthenia, lethargy

*Rash includes rash, rash macular-papular, rash erythematous, rash purpuric, rash macular, exfoliative dermatitis

*Clinically relevant adverse reactions in <10% of patients who received UKONIQ included urinary tract infection (9%), dyspepsia (7%), pneumonia (6%), steatosis (3%), colitis (2%), pneumonitis (<1%), and leukopenia (<1%).

*Upper respiratory tract infection includes Upper respiratory tract infection, sinusitis, rhinosinusitis, rhinitis

*Diabetes includes hyperglycemia, diabetic gastroparesis, diabetic ketoacidosis

*Serious adverse reactions in <10% of patients who received UKONIQ included urinary tract infection (9%), dyspepsia (7%), pneumonia (6%), steatosis (3%), colitis (2%), pneumonitis (<1%), and leukopenia (<1%).

Table 4: Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Any Grade (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

*Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading system.
8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action (see Clinical Pharmacology (12.1)), UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate a drug-associated risk to a fetus. In animal reproduction studies, administration of umbralisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and abnormal fetal development at maternal exposures (AUC) comparable to those in patients during the recommended dose of 800 mg (see Data). Males with MZL were required to have received at least one prior therapy, including an anti-CD20containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Patients receiving UKONIQ 800 mg orally once daily until disease progression or unacceptable toxicity. Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range: 15.0 to 28.7 months). Efficacy results are shown in Table 6.

Table 5: Efficacy Results in Patients with MZL (Study 205)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Total (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>34 (49)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>45 (65)</td>
</tr>
<tr>
<td>DOR</td>
<td>2.33</td>
</tr>
</tbody>
</table>

CR, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; NL, not evaluable; PR, partial response.

*For IRC, according to Revised International Working Group Criteria. §Based on Kaplan-Meier estimates. ¶Denotes censored observation

8.2. Lactation

Risk Summary

There are no data on the presence of umbrelasib in human milk or the effects on the breastfed child or milk production. Because many drugs are excreted in human milk, advise females of reproductive potential not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential

UKONIQ may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)).

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating UKONIQ. Male contraception

Females

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

Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose.

Infertility

Males

Based on the findings from mice and dogs, UKONIQ may impair male fertility (see Nonclinical Toxicology (13.1)). Trend for reversibility was noted in dogs 30 days after the last dose.

8.4. Pediatric Use

Safety and effectiveness of UKONIQ have not been established in pediatric patients.

8.5. Geriatric Use

Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 54% of patients were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% in patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age and older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance (Ccr) > 30 to 89 mL/min estimated by Cockcroft-Gault equation) (see Clinical Pharmacology (12.3)). UKONIQ has not been studied in patients with severe renal impairment (Ccr < 30 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN)) and moderate hepatic impairment (total bilirubin > 1 to ≤ 1.5 × ULN and any AST or ALT > 2.5 × ULN and any AST). UKONIQ has not been studied in patients with severe hepatic impairment (total bilirubin > 1 × ULN and any AST). Clinical Studies

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.

8.8. Monitoring

Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a fever or any signs or symptoms of infection (e.g., fever, chills, weakness) (see Warnings and Precautions (5.1)).

Neutropenia

Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs or symptoms of infection (see Warnings and Precautions (3.2)).

Diabetes or Noninfectious Cytosis

Advise patients that they may experience loose stools or diarrhea and should contact their healthcare provider with any persistent or worsening diarrhea. Advise patients to maintain adequate hydration (see Warnings and Precautions (5.2)).

Severe Cutaneous Reactions

Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a new or worsening skin rash (see Warnings and Precautions (5.3)).

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential 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 (5.7)).

Hepatotoxicity

Advise patients that UKONIQ may cause significant elevations in liver enzymes. Advise patients to report any signs or symptoms of liver dysfunction (jaundice (yellow eyes or yellow skin), abdominal pain, bruising, or bleeding) (see Warnings and Precautions (5.4)).

15.5 months).
INFIGRATINIB (TRUSELTIQ) REPRESENTS a strong option for previously treated patients with locally advanced or metastatic cholangiocarcinoma whose tumors harbor FGFR2 fusions or rearrangements, according to Sameek Roychowdhury, MD, PhD. Next steps for research will be focused on further leveraging the activity observed with the agent and gaining a better understanding of other alterations within the FGFR pathway to develop additional targeted options for rarer subsets.

Results from a multicenter, open-label, single-arm, phase 2 study (NCT02150967) showed that at a median follow-up of 10.6 months (range, 6.2-15.6), the FGFR inhibitor infigratinib elicited an objective response rate of 23.1% (95% CI, 15.6%-32.2%), with 1 confirmed complete response and 6.2% of patients achieving partial responses (PRs).1 Results from the trial supported the May 2021 FDA approval of infigratinib for use in patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring an FGFR2 fusion or rearrangement.2

“There are going to be more novel genetic alterations in FGFR [to examine],” Roychowdhury said. “As such, there are going to be more patients [beyond] those who have cholangiocarcinoma, [those with] other cancer types, who have other mechanisms to activate the FGFR pathway and could derive benefit from FGFR inhibitors.”

In an interview with OncologyLive®, Roychowdhury, medical oncologist, associate professor in the Department of Internal Medicine and the Department of Pharmacology at The Ohio State University in Columbus, discussed the efficacy and safety data reported with infigratinib in FGFR2-positive cholangiocarcinoma, the nuances of treatment with the agent, and ongoing research efforts to further improve outcomes in this population.

Please provide some background information on infigratinib and what sets it apart from other agents utilized in cholangiocarcinoma, such as pemigatinib (Pemazyre).

ROYCHOWDHURY: We have learned that a fraction, approximately 15%, of patients who have intrahepatic cholangiocarcinoma will have FGFR2 gene rearrangements, sometimes referred to as fusions. Several companies over the past 7 years have developed and studied FGFR inhibitors, [which are] small molecule inhibitors for patients with FGFR-altered cancers. Over the years, [these agents have been investigated in] all solid tumors [as part of] the first phase 1 trials.

Then, disease-focused clinical trials [were done] for cholangiocarcinoma and urothelial cancer. We have seen several drug approvals, the first [being] erdafitinib [Balversa] for [patients with] urothelial cancer with FGFR alterations, followed by pemigatinib [Pemazyre], which was examined [in patients with] cholangiocarcinoma harboring FGFR2 alterations. Most recently, we saw data become mature and [support] the FDA approval of infigratinib for [patients with] FGFR2-positive cholangiocarcinoma.

We are seeing that many patients can benefit [from infigratinib]. We have seen a safety profile that is unique to the class of FGFR kinase inhibitors. We are excited to now be able to offer these agents to patients with FGFR-positive cholangiocarcinoma. [These advancements have] also placed a greater emphasis on the need to [give these patients diagnoses] early on, to ensure they receive adequate genetic testing that can find FGFR alterations in cholangiocarcinoma. In addition to FGFR inhibitors, these patients could benefit from other targeted therapies. As such, comprehensive genetic testing for cholangiocarcinoma is important.

One important pearl [of wisdom] about cholangiocarcinoma is that, many times, it can present as something [like] poorly differentiated cancer and the pathologist will not [give the patient a diagnosis of] cholangiocarcinoma. A lot of times, however, cholangiocarcinoma is just that: poorly differentiated. The clinical presentation of having a large dominant liver mass, a few smaller liver lesions, an elevated CA 19-9, and no pancreas lesions is cholangiocarcinoma. We want to ensure that these patients undergo genetic testing so that we can make the [correct] diagnosis and offer them appropriate treatments.

Shifting specifically to the pivotal phase 2 trial examining infigratinib, what was the objective of this research and what was found? The study was meant to identify patients with FGFR-altered cancers. Most patients had FGFR2 alterations. This was a single-arm, open-label study, and all patients received infigratinib. We were looking specifically at the overall response rate and the disease control rate [achieved with the agent].

We were quite impressed to see that many of our patients benefited [from the agent, with] some [achieving] stable disease and a smaller number of patients [achieving] PRs. Interestingly, even stable disease can be very durable. I have patients with [stable] disease who, in some cases, do better or live longer than those who achieved PRs [to treatment]. The depth of their response is not necessarily predictive of their overall survival. We are excited to see that patients are also benefiting [from this drug] outside of the clinical trial.

Did the number of prior lines of therapy received have an impact on benefit derived with the agent? The patients in the study had to have received at least 1 prior line of therapy, which was usually some [type of] platinum-based or gemcitabine-based chemotherapy, which is a standard of care for cholangiocarcinoma. Some patients may have received up to 3 or 4 prior lines of therapy.

Following the principles of oncology practice, the number of lines of therapy [received] can predict someone’s ability to get through more therapy. More lines of therapy can make it harder for [a patient] to benefit and tolerate therapy. However, the good news is that even patients who have received many lines of prior therapy can still derive benefit from infigratinib or [other] FGFR inhibitors, so we are fortunate to see that.

What has been learned about time to response with infigratinib? One of the important nuances is that sometimes the response to therapy can be slow. After 2 months of therapy is when we typically will consider a new CT scan as part of a clinical trial or standard practice. [However,] we might not see many changes by 2 months. By waiting a little bit longer, [say] 4 or 6 months, we may start to see a slow change in response. It may not meet the criteria for PR, but we do see slow responses with [infigratinib] in patients with cholangiocarcinoma, which probably has something to do with the biology of FGFR-positive liver cancers.
What does the safety profile of the agent look like? What should your colleagues be aware of when using this drug?

Many of the patients experienced similar toxicities [to what has been seen with other FGFR inhibitors]. Some of the unique adverse effects [AEs] experienced with FGFR inhibitors include hyperphosphatemia, which is an expected on-target effect [because] the drug inhibits FGFR2, but it also inhibits FGFR1 and FGFR3. It is thought that FGFR1 affects the body’s management of phosphorus, so we see and expect an elevation of phosphate levels. We recommend managing [that effect] with phosphate binders.

In the study, we [also saw] patients with hypophosphatemia, where [phosphate levels were] low; that’s an AE [that can result from the over-utilization of] phosphate binders, which drive phosphate [levels] down. It is not a problem to worry about and can be easily fixed by adjusting the phosphate binder. Some of the other unique AEs [experienced with] this drug class include mucositis, dry eyes, and paronychia, which is brittleness and tenderness of the nails. These chronic accumulative AEs can be managed with dose reductions.

Unfortunately, some of these AEs do not go away completely but they are not life-threatening. [These toxicities] do have quite a bit of an effect on quality of life, but sometimes we are just happy to be able to control the liver cancer for 18 months and some nail damage [can be tolerated]. Perhaps we will [continue to] learn a little bit more [about this as we get more experience]. These are the first drugs [to target] FGFR. We are [continually] learning to [more effectively] manage these AEs. Maybe we will be able to reduce some of these toxicities moving forward if we learn and study [them] further.

Please explain on what management looks like for those AEs in practice. Do AEs, such as the eye toxicities, require multidisciplinary care?

We do expect to see some eye toxicities, such as dry eyes. We can see fluid or swelling behind the retina. Regular examinations with the ophthalmologist are recommended to help observe these AEs. Some of [these toxicities] do not come with [visible] symptoms, so [patients] may have fluid behind the retina and that may [not be observable] as opposed to the expectation of blurred vision. Many of these can be managed with dose reductions. Having a low threshold to reduce these doses is a good idea so that we can minimize some of the toxicities. However, regular eye exams are recommended for most of the FGFR inhibitors that are approved [for use] today.

What has been the impact of the FDA approval of infigratinib on the cholangiocarcinoma treatment paradigm? What should be understood about the indication?

Having more options for our patients with cholangiocarcinoma is always a great thing. We have seen a growth in drug development in this area of both FGFR-positive cholangiocarcinoma as well as other cancers with FGFR positivity. We are also still learning about genetic changes in FGFR that can activate FGFR signaling.

A recent paper published in Cancer Discovery [looked at] some mutations that are part of the extracellular domain of FGFR, and I have had several patients with similar mutations who respond to FGFR inhibitors. These [subsets] are not included in the FDA labels regarding urethelial carcinoma or cholangiocarcinoma. As such, it is important for us to see these patients and get them on clinical trials to collect [the necessary] data [on the benefit of these agents].

We have more to learn about FGFR genetics, we have more patients who can benefit [from these inhibitors], and thankfully many new companies are entering the space. [Bearing in mind] the patients who have their cancer progress, we have now cataloged over 15 mutations that are acquired and can render the cancer resistant to these first-generation FGFR drugs. The more people who get in this game to help us to develop better drugs, the better [outcomes] our patients will [have]. A healthy amount of competition in the marketplace is good for all of us—patients, doctors, and the field overall. We are glad to see a lot of interest in FGFR drug development.

Regarding next steps for this agent, do you foresee it moving into the first-line setting? Is that under investigation now?

Several clinical trials are happening right now in cholangiocarcinoma that are looking at gemcitabine and platinum-based chemotherapy vs an FGFR inhibitor. We look forward to seeing read-outs of [those efforts to gain insight into] which [therapy] should be utilized first.

Another twist to that idea is whether we should be considering chemotherapy and a kinase inhibitor together, or whether should we be considering them in a cyclical way, so alternating therapy to forestall drug resistance and potentially limit the amount of cumulative toxicity from one [approach] or the other.

If you cycle back and forth between a chemotherapy and a targeted inhibitor, you could try to limit some of the cumulative toxicities, such as cytopenia and other [AEs] that come with FGFR inhibitors. These are all exciting [areas of exploration] for the next couple years.

What is your take-home message regarding this research?

First, besides FGFR2, we do know that there are other activating alterations in FGFR receptors like FGFR1 and FGFR3, and this is not limited to fusions. Whenever you see a patient with cancer involving the liver and you see something related to FGFR, [it is important] to ask yourself whether that is a driver mutation.

In the next couple years, we would like to see some of these patients who have received a standard-of-care FGFR inhibitor, such as infigratinib or pemigatinib, get referred to tertiary medical centers because we have several FGFR inhibitors that are second generation. We need to get these patients into those clinical trials. We need better options; [these patients] eventually experience progression of their cancer.

[Because this is] a rare cancer, the number of patients who are [eligible] for such studies is small. As such, we need everyone’s help to get patients into these new clinical trials so that we can bring more therapies [into the armamentarium and provide even better] standard-of-care [approaches to this population].

REFERENCES


Current Management Strategies for Desmoid Tumors Are Marked by Less Surgery, More Systemic Options

by Jessica Hergert

**DESPITE THEIR RARITY**, the management of desmoid tumors has been an area of significant clinical change as the field has shifted away from aggressive surgical interventions to active surveillance and systemic therapies that have less morbidity for patients, said a group of experts during interviews with OncLive®, adding that the field will continue to evolve as treatment-informing tools emerge to guide decisions and improve outcomes.

“We want to turn this into a disease that is amenable with systemic therapies rather than surgery,” stated Alexander J. Lazar, MD, PhD, professor in the Department of Pathology of the Division of Pathology/Lab Medicine, academic surgical pathologist, director of the Sarcoma and Melanoma Clinical Genomics Program, and director of the Selective (Soft Tissue) Pathology Fellowship Training Program at The University of Texas MD Anderson Cancer Center in Houston.

Lazar was joined by:
- R. Lor Randall, MD, FACS, The David Linn Endowed Chair for Orthopaedic Surgery; professor and chair, Department of Orthopaedic Surgery, University of California (UC) Davis Comprehensive Cancer Center, UC Davis Health
- Breelyn Wilky, MD, director, Sarcoma Medical Oncology; deputy associate director, Clinical Research, University of Colorado Medicine, Aurora
- Gina Z. D’Amato, MD, associate professor and assistant director of clinical research, Department of Medicine, Sylvester Comprehensive Cancer Center, University of Miami Health System, Florida
- Ravin Ratan, MD, MEd, assistant professor, Department of Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

The experts highlighted key challenges that remain in the management of desmoid tumors, emerging systemic options that are positioned to transform the paradigm further away from surgical interventions, and the importance of getting second opinions in this space.

**What current challenges exist regarding identifying and diagnosing desmoid tumors?**

**LAZAR:** The big challenge with desmoid tumors is that they are rare. Not everybody has a lot of experience with them, so that creates some challenges [in the accuracy and timing of the diagnosis]. The other challenge is that, under the microscope, they look a lot like reactive fibrosis or a scar. Unless one is thinking about a desmoid tumor and including it in the differential diagnosis, we may not think about it as a diagnosis. We may think it is the reactive part of another [ongoing] process.

**RATAN:** Desmoid tumors are very rare, in the range of a couple hundred cases a year in the United States. In practical terms, that means that most doctors a patient interacts with don’t see these often or might not know they exist. If a patient in the community is noticing swelling in an arm or leg, pain, stiffness, or any of the myriad of symptoms desmoid tumors can present with, it is likely that the doctor caring for them is not going to jump to a desmoid tumor [diagnosis]. The reality is that they probably shouldn’t because most of those aches and pains are going to be conditions that are self-limited and don’t require immediate work-up. However, patients often have to persist and raise these symptoms over and over again before they are taken to a place for imaging or further work-up that results in the diagnosis of a desmoid tumor.

The other pathway we see to diagnosis is a patient who has imaging done for some other reason, which incidentally finds a mass diagnosed as a desmoid tumor. That is one issue. There isn’t a high index of suspicion ever for desmoid tumors because symptoms are often vague.

The second issue is once a mass is diagnosed and removed or biopsied, making sure that specimen gets put in front of a pathologist who has some expertise in the diagnosis of soft tissue tumors or desmoid is important. That doesn’t happen uniformly. By the time someone makes it to me at a specialty center, they usually come with a diagnosis, but that diagnosis can take months or longer.

**RANDALL:** If a patient has a known desmoid tumor, the first bridge to cross is whether they have an APC mutation and whether they are at risk for Gardner syndrome or multiple desmoid fibromatoses and polyposis. That is hurdle No. 1. We know that patients with Gardner syndrome [can] have multiple relapses...because they [can] have multiple desmoids. Those patients need to be watched more aggressively than patients who do not have the mutation. Genetic counseling for patients with a solitary desmoid tumor, especially if they have a history of colon cancer in the family, is strongly recommended.

**What challenges exist in terms of managing patients with these tumors?**

**WILKY:** The first inclination most people have when they are told they have a desmoid tumor is to [have it cut out]. The problem is that doing surgery on desmoid tumors can trigger recurrences in a fair number of patients; as many as up to 50% of tumors can recur after surgery. It’s important not to necessarily jump into surgery and to, instead, learn about different [treatment] options. Some desmoid tumors can regress on their own. [Approximately] 20% of desmoid tumors will simply go away by doing nothing. The biggest [issues for patients] are to find an expert [on soft-tissue sarcoma], have their individual case analyzed [by a multidisciplinary team], and learn about the whole spectrum of options before jumping into a surgery or other procedure.

**LAZAR:** The challenge right now in the field is determining at what point and in which cases do we decide to go with aggressive treatment and in which we continue watchful waiting. We are hoping that some of the new oral or intravenous systemic therapies can make a real difference for these patients in the absence of surgical management, which can sometimes be mutilating.

**How often do you see patients with a misdiagnosed desmoid tumor? What are some best practices for avoiding that?**

**LAZAR:** There can sometimes be misclassification, but probably more importantly, we have seen a delay in diagnosis because it takes people awhile to come up with the idea [of desmoid tumors] or to [transfer the
case] to someone who has more experience with this disease. Because we have a lot more tools to differentiate different types of spindle-cell neoplasms, the number of misdiagnoses has probably gone down over time. However, there is still some delay in diagnosis because of challenges in recognizing this disease as a definitive tumor as opposed to a reactive process.

**WILKY:** If a patient is told that they have a very rare tumor, [such as] a desmoid tumor, the first thing they need to do is have their tissue reevaluated at a [center specializing in soft-tissue sarcomas]. That means sometimes asking for a second opinion or asking whoever did their biopsy to send it to an expert center. I have had patients with desmoid tumors who were told they have a full-blown sarcoma and needed chemoradiation. I’ve also had patients who were told they had benign disease when they did have a full-blown sarcoma that required additional therapies. This goes for any diagnosis of a cancer, precancer, or benign tumor—second-opinion review by an expert center for rare diseases is critical to ensure the diagnosis is accurate.

**What is your current treatment approach for these patients? Has it changed with recent advancements in available therapies?**

**D’AMATO:** Old school thinking was surgery. Now we have specific guidelines that were put together by the Desmoid Tumor Research Foundation. Sarcoma experts recommend we limit surgery after observation to an area that would not cause any long-term dysfunction. The tumor might die out over time, but once we remove something surgically, we can’t bring it back. We don’t want to leave someone with a deficit.

If we do medical management, adverse events [AEs] can be reversed and, to our knowledge, we don’t see many long-term complications with most of our systemic therapies. Some [systemic options] can cause long-term complications, but they are much less than that of surgery. Systemic therapy is recommended based on where the tumor is located, how symptomatic the patient is, and whether [the desmoid tumor] is potentially organ- or life-threatening.

Mesenteric masses are probably the most dangerous, per se, and would be [treated with] sorafenib [Nexavar] in the first-line setting or chemotherapy if it is bothersome [to the patient].

The sorafenib dose is 400 mg, which is different from the cancer dose of 800 mg. It tends to be well tolerated although there are certain AEs, such as hand-foot-skin reaction, rash, elevated blood pressure, nausea, and diarrhea; however, most of those can be controlled with concomitant medications or stopping the drug for a bit then restarting. We don’t know the long-term complications of these drugs because they haven’t been around long enough.

With chemotherapy, that is a different situation. Those patients can have more AEs, including pancytopenia, infections, hair loss, and secondary cancers about 5 years [after stopping chemotherapy]. We have to think about [those AEs] and [reserve chemotherapy] for when [a desmoid tumor] is really threatening, like intra-abdominal tumors or tumors near the neck that can press on important structures.

**In terms of treatment selection, what factors need to be considered?**

**RANALLD:** Don’t make the treatment worse than the disease. Historically, we used to think of desmoid tumors as cancers and [use] aggressive [regimens to gain] local control at any expense. We dealt with the repercussions after, but sometimes we mutilated some of these patients all for the concept of a negative margin and left them with a worse problem than when they started.

Sometimes, a very well-intentioned but inexperienced surgeon in the realm of desmoid tumors treats these patients aggressively with surgery and radiation, leaving them left with disfigurement, pain, and identity issues. Don’t make the treatment worse than the problem. The take-home message for medical oncologists is to slow down, talk to someone who has experience with desmoid tumors, and then have a very informed discussion with the patient.

Historically, surgery plus or minus radiation therapy was the best treatment modality for patients with desmoid tumors. Now, surgery plays an important but less broad role in the management of desmoid tumors. Often, someone will come in with a solitary desmoid tumor. The first-line option is to watch it if it isn’t bothering them to look for progression. If it looks like it is progressing, there are a variety of noncytotoxic and cytotoxic medical therapies that can be offered.

**LAZAR:** The most important consideration [for patients] with desmoid tumors is the course of the disease. If the patient has stable disease, they can be safely watched. If it is a disease that is rapidly progressing and causing other problems in terms of pain or dysfunction, we have to quickly think about other interventions we can do, such as surgery, radiation, or systemic therapies.

**What systemic options have demonstrated efficacy in this patient population?**

**WILKY:** Sorafenib was studied in a phase 3 trial [NCT02066181] for [patients with] desmoid tumors, which was amazing because this is a rare disease, but we were able to do a phase 3 study. That study was a slam dunk. Clearly, this is an active drug. There are AEs with [sorafenib], but many times, this is a great option for patients to consider.

**Please speak to some of the emerging systemic therapies we’re seeing in this space.**

**D’AMATO:** We have some new clinical trials with gamma-secretase inhibitors [GSIs]. We have DeFi, the phase 3 clinical trial [NCT03785964] comparing nirogacestat with placebo. That trial is currently closed to enrollment, so we are anxiously awaiting the results of that.

**WILKY:** We are all excited to see if [nirogacestat] could potentially be [a] drug approved [for patients with] desmoid tumors. [Nirogacestat] looked promising in older [data from] phase 2 studies and the [phase 3 data] is about to reach maturity. Interventional approaches, such as cryoablation where we can freeze the tumor, have also become exciting. These are areas of active investigation.

**LAZAR:** Some direct inhibitors of β-catenin, which is the gene that is normally mutated in these tumors, [are under investigation]. β-catenin drives oncogenesis, and some direct inhibitors of that pathway may have some efficacy as well [for patients with desmoid tumors].

**RATAN:** There is another drug called tegavintin, which is also being investigated [for] the treatment of desmoid fibromatoses. That drug works a little bit differently as it is not a GSI. It is a drug that seems to directly look at the interaction between β-catenin and TBL1, which stabilizes β-catenin. Accumulation of β-catenin [results in cell proliferation]. Tegavintin seems to reverse that accumulation [of β-catenin] through direct inhibition between β-catenin and a stabilizing protein.

**What are the most pressing unmet needs in this space, and how are they being addressed?**

**WILKY:** In general, the types of desmoid tumors that are the hardest to deal with are those that occur in conjunction with a disease called familial adenomatous polyposis [FAP]. Most desmoid [tumors] are sporadic and we don’t know what causes them. They [can] occur in one place and are sometimes associated with an injury [or surgical procedure]. However, people with FAP have an inherited tendency to develop desmoid tumors. The problem is that they can get multiple desmoids in multiple locations, often inside the abdominal cavity. These tumors can be very difficult to treat or manage.

Those are the patients who I’ve had the biggest challenges with creating meaningful quality of life because they go through multiple surgeries and may have long-term issues from bowel obstructions or resections. Our hope is that newer drugs will prove to be just as effective in that group of patients, but that is an area where we still have big challenges to help our patients live better lives and control the disease.

**What does the future look like in this space?**

**LAZAR:** We have a lot more tools for [desmoid tumors] than we used to. Some of these new systemic therapies have demonstrated efficacy or are currently in clinical trials, which will give us new tools. We now know also that watchful waiting can be an effective way to follow and manage these patients.

What would be helpful are algorithms to evaluate patients so that [we] can identify optimal treatment strategies for patients. Right now, the default, unless we can’t do otherwise, is watchful waiting. Then, as the biology of the disease reveals itself, we start thinking about what interventions we could use to benefit the patient.
PATIENT EDUCATION IN ONCOLOGY can often be daunting and complicated for clinicians and patients. Traditional patient education methods such as videos, handouts, and reviewing standard medical imaging often fall short in conveying complex information. As a result, 3-dimensional (3D) virtual reality (VR) experiences are increasingly being explored as an appealing alternative method of imaging review for patients with cancer.¹

"Patients struggle to know what’s happening within their own bodies,” said Douglas E. Holt, MD, a radiation oncologist at Gamma West Cancer Services in Idaho Falls, Idaho, in an interview with OncologyLive®. “They’re making decisions being somewhat or quite uninformed about what’s going on. VR [provides an] opportunity to help patients be engaged in their own disease process and on decisions of the future of their cancer [journey].”

Holt developed and implemented a program to demonstrate how VR can improve patient education.¹ He received the 2021 Association of Community Cancer Centers (ACCC) Innovator Award for his work and presented the findings at the ACCC 38th (Virtual) National Oncology Conference in November 2021.²

Although most patients want to be as informed as possible about their condition, studies have found that up to 80% of information presented to patients by clinicians is forgotten almost immediately. As much as 50% of the information that is remembered by patients is retained inaccurately, and patient recall tends to be poorer as greater amounts of information are presented. These issues can be worsened by factors including poor health literacy among patients, the amount and complexity of information presented, language barriers, and the stress a patient is feeling because of the diagnosis.¹,²

By itself, verbal discussion between patient and clinician has been found to be the least effective educational method. Standard medical imaging contains most of the information patients need to understand their condition but is difficult to interpret without years of training. Because of the shortcomings of current patient education strategies, patients often lack the context and understanding to participate in discussions about their condition and to make decisions concerning their care.³

“Medical imaging has a lot of the information right there; it’s just in a form [that] patients can’t understand,” Holt said. “VR is a way that clinicians can intuitively show someone their own body, where the problem is with their tumor, and the extent of their disease. [Clinicians] can show patients why they are having the symptoms they’re having and then help them understand what their treatment would look like.”

MEETING PATIENTS HALFWAY

Holt sought to address the disconnect in patient education in oncology by using VR in a proof-of-concept study. The goal of the trial was to identify and address the technical challenges of implementing VR in the clinic and to objectively measure subjective patient experiences with the technology. Holt partnered with clinical psychology professionals and a psychometrician utilizing a mixed-methods approach consisting of quantitative surveys and qualitative semi-structured interviews. A qualitative analysis was also performed to identify commonly shared themes among patients.²

The median age of the 25-patient population was 59 years (range, 11-95). The population included patients with tumor sites in the central nervous system, head and neck, breast, thorax, gastrointestinal tract, and pelvis. The median time from diagnosis to the VR education experience was 5 months (interquartile range, 3-19). Each VR session lasted approximately 5 to 7 minutes and included patients and their caregivers.

During the session, patients wore a VR headset and used 2 hand controls to navigate the experience. The system combined individual slices of medical images to create a 3D rendering.
of the patient’s tumor site that could be viewed from a third-person perspective. Patients could freely move about, rotate, and zoom in and out on their tumor to get a better understanding of its size, location, and potential impact on neighboring organs.

After the VR session, patients rated their understanding of their tumor/disease at a mean level of 9.2 out of 10, with a 10 being full understanding, compared with 5.6 before the session (P < .0001).

Patients were also asked to identify their preferred method for medical imaging review; 96.9% of patients chose VR vs 3.1% who selected imaging review via a standard computer screen. Members of the study population ranked what they considered the top educational tool for understanding their disease after the VR session. VR received the top ranking 83.3% of the time, followed by verbal discussion (8.3%), self-research (5.6%), and drawings (2.8%).

VR also outperformed imaging review via a standard computer screen in an understanding of disease and treatment analysis on a scale of 1 to 3, with 3 being full understanding. The mean patient rating with the VR experience was higher than that for the computer screen in every category surveyed: tumor appearance (2.8 vs 1.3, respectively), tumor size (2.8 vs 1.4), tumor location (2.9 vs 1.5), organs adjacent to tumor (2.9 vs 1.2), tumor-related symptoms (2.7 vs 1.6), treatment rationale (2.9 vs 2.0), radiation target (3.0 vs 2.0), and radiation toxicity (2.8 vs 1.3). On the same 3-point scale, VR also outperformed the computer screen when patients rated the experience for reduction in anxiety (2.2 vs 1.1), feeling of engagement in health care (2.8 vs 1.5), and satisfaction (2.9 vs 1.0). Investigators asked patients to rate the level of importance of VR in viewing their tumor/disease. The method attained a mean score of 9.1 out of 10.

Patients gave additional feedback on the VR imaging review on a 5-point scale from “strongly disagree” to “strongly agree.” Most patients strongly agreed (78.9%) or agreed (18.4%) that they were comfortable with VR for medical imaging review; 2.7% strongly disagreed.

The statement, “important for VR experience to be shared via multiuser platform” was strongly agreed with by 64.9% of patients and agreed with by 32.4% of patients. Most patients also strongly agreed with the statements “VR increased trust in physician and treatment team” (75.0%), “want VR to be used in own healthcare in future” (81.6%), and “VR should become standard-of-care in imaging review” (78.9%). Patients did not strongly disagree or disagree with any of the other statement options.

“The general response [to VR education] was amazingly positive,” Holt said. “A lot of patients would say something [such as], ‘that was incredible,’ or ‘that was amazing.’ With cancer consultations, those are not words you usually hear.”

Holt noted that despite the overwhelmingly positive patient reaction, the VR approach is still far from being the standard of care in oncology imaging review. The current form is not accessible to most patients with cancer and is not scalable. According to Holt, issues affecting the scalability of the technique include many cancer care facilities lacking adequate software and hardware, challenges with sterilization, and the long preparation time with patients that is needed for each session.

There are several other ongoing or completed studies aiming to implement VR approaches in cancer care. Liimatainen et al created a novel interface that utilized VR to visualize 3D histology data. Through an interactive VR application, the user can set visualization properties, select different samples and features, and interact with various objects, which is not possible in the traditional 2-dimensional image view used in digital pathology.

In another study, Wang et al constructed an application that ran on a commercially available stand-alone VR headset, allowing patients to view a virtual simulation of radiotherapy treatment. The patient’s computed tomography simulation data were converted into a 3D translucent virtual human shown lying on a treatment table as visible yellow radiation beams were delivered to the target volumes in the patient. Among the 43 patients with cancer enrolled in the study, 74% strongly agreed that the session gave them a better understanding of how radiotherapy would be used to treat their disease. Of the 21 patients who expressed any anxiety about radiotherapy prior to the study, 57% said that the VR session helped reduce their anxiety about undergoing treatment.

“The future for patient education in oncology and the rest of medicine is VR,” Holt concluded. “It’s a format that [allows] patients to understand intuitively what’s happening within their own bodies. The next steps would be to do larger studies, in oncology and then outside of oncology, to really be able to evaluate some of the other tangible benefits of this to patients [beyond] education.”

REFERENCES


**INDICATION**

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:  
**First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab**

In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

There are no contraindications for LYNPARZA.

**WARNINGS AND PRECAUTIONS**

**Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):** Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≥Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

**Pneumonitis:** Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

**Females**

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

**ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab**

Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab compared to a ≥5% frequency for placebo/bevacizumab in the first-line maintenance setting for PAOLA-1 were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%) and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency...
**CONTRAINDICATIONS**

Do not start LYNPARZA until patients have recovered from hematological and other toxicities, including radiotherapy.

Chemotherapy with platinum agents and/or other DNA-damaging agents (range: <6 months to >10 years). All of these patients had previous genomic instability. Select patients for therapy based on an FDA-approved BRCA homologous recombination deficiency (HRD) positive status defined by platinum-based chemotherapy and whose cancer is associated with peritoneal cancer who are in complete or partial response to first-line monotherapy, and some cases were fatal. If patients present with new symptoms, advise the patient to a hematologist for further investigations, including bone marrow biopsy.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer to a hematologist for further investigations, including bone marrow biopsy.

**INDICATION**

- **HRD-POSITIVE**

**DISCOVER THE**

In combination with bevacizumab for the maintenance treatment of ovarian cancer in patients who have had a complete or partial response to first-line platinum-based chemotherapy.

*Select patients for this indication based on an FDA-approved companion diagnostic.1*

**PAOLA-1**

**~50% WERE HRD POSITIVE2**

**PRESPECIFIED EXPLORATORY ANALYSIS1,3:**

- **LYNPARZA + BEVACIZUMAB**
  - **3.1 YEARS mPFS**
  - **~1.5 YEARS mPFS**

Median PFS was 37.2 months with LYNPARZA + bevacizumab (n=255) and 17.7 months with bevacizumab + placebo (n=132); HR=0.33; 95% CI: 0.25–0.45

_Data based upon a prespecified exploratory subgroup analysis, which was not controlled for Type 1 error. HRD status was not a stratification factor in PAOLA-1._4

**STUDY DESIGN1-3**

PAOLA-1 was a phase 3 trial of women with advanced ovarian cancer that enrolled patients regardless of surgical outcome or BRCA mutation status following response to first-line platinum-based chemotherapy with bevacizumab. Patients were randomized 2:1 (N=806) to receive LYNPARZA tablets 300 mg BID in combination with bevacizumab 15 mg/kg (n=537) or placebo BID in combination with bevacizumab 15 mg/kg (n=269).

Bevacizumab was administered every 3 weeks for a total duration of up to 15 months, and LYNPARZA or placebo treatment was administered for up to 24 months or until disease progression or unacceptable toxicity.

The primary endpoint was the investigator-assessed PFS. Prespecified exploratory analyses included PFS in predefined subgroups, including HRD status and BRCA mutation status. PFS within HRD-positive patients served as the basis of the FDA-approved indication.

There’s MORE to learn about LYNPARZA. Explore the data at MoreTo3.com

**IMPORTANT SAFETY INFORMATION (Cont’d)**

Compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%) and headache (14%). In addition, venous thromboembolic events occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the first-line maintenance setting for PAOLA-1 were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%) and decrease in platelets (35%).

**DRUG INTERACTIONS**

_Anticancer Agents:_ Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

**CYP3A Inhibitors:** Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

**CYP3A Inducers:** Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

**USE IN SPECIFIC POPULATIONS**

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production.

**Pediatric Use:** The safety and efficacy of LYNPARZA have not been established in pediatric patients.

**Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

**Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (Clcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (Clcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (Clcr ≤30 mL/min).

You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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

BID = twice daily; CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; mPFS = median progression-free survival.

**References:**


LYNPARZA is a registered trademark of the AstraZeneca group of companies. ©2021 AstraZeneca. All rights reserved. US-53362 S/21
First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer

Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and who have a germline or somatic BRCA mutation. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1) in the full Prescribing Information].

Maintenance Treatment of Recurrent Ovarian Cancer

Lynparza is indicated for the maintenance treatment of adult patients with recurrent ovarian epithelial, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Lynparza is indicated in combination with bevacizumab for the maintenance treatment of recurrent or refractory HRD-positive ovarian cancer in adult patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy and bevacizumab [see Clinical Studies (14.3) and the full Prescribing Information].

Advanced Germline BRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1) in the full Prescribing Information].

Dosage and Administration

Patient Selection

Information on FDA-approved tests for the detection of germline mutations is available at http://fda.gov/companiondiagnostics.

Select patients for therapy based on the presence of deleterious or suspected deleterious germline HRD gene mutations, including BRCA mutations, or germline instability based on the indication, biomarker, and disease status.

Table 1 Biomarker Testing for Patient Selection*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Biomarker</th>
<th>Sample Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line maintenance treatment of germline or somatic BRCA-mutated ovarian cancer</td>
<td>BRCA1m, BRCA2m</td>
<td>Tumor, Blood, Plasma (ctDNA)</td>
</tr>
<tr>
<td>First-line maintenance treatment of BRCA-mutated ovarian cancer in combination with bevacizumab</td>
<td>BRCA1m, BRCA2m</td>
<td>Tumor, Blood, Plasma (ctDNA)</td>
</tr>
<tr>
<td>Maintenance treatment of recurrent ovarian cancer</td>
<td>N/A</td>
<td>requirement for biomarker testing</td>
</tr>
<tr>
<td>Advanced gBRCAm ovarian cancer</td>
<td>N/A</td>
<td>X</td>
</tr>
</tbody>
</table>

* For biomarker testing as a tissue sample biomarker, a confirmatory test is recommended upon initial testing negative or uncertain, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food. If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablets.

In clinical studies enrolling 2011 patients with various cancers who received Lynparza as a single agent (see Adverse Reactions (6.1) in the full Prescribing Information), the incidence of proteinuria during the first 4 weeks after dosing was 0.8% (N=2011). If patient, present with new or worsening respiratory symptoms such as dyspnea, cough, or fever, or a radiologic abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the respiratory symptoms. Lynparza treatment is reinitiated if the source is determined to be unrelated to Lynparza and the patient is appropriately evaluated.

Lynparza can cause fatal harm when administered to a pregnant woman based on the mechanism of action and findings in animals. In a animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity of exposures below but near the minimum human dose of 300 mg twice daily. Approve pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise female reproductive potential patients of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Lynparza is contraindicated in breastfeeding women.

Breastfeeding Women

Advise women not to breastfeed.

Preclinical Toxicology

Myelodysplastic Syndrome/Acute Myeloid Leukemia

In nonclinical studies, olaparib caused myelosuppression, the most common adverse reactions in >10% of animals were nausea (60%), fatigue (50%), anemia (34%), vomiting (28%), diarrhea (24%), dyspepsia (23%), and dysgeusia (21%).

Table 1 Biomarker Testing for Patient Selection*

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* For biomarker testing as a tissue sample biomarker, a confirmatory test is recommended upon initial testing negative or uncertain, if available.
Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19.

† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

25% of Patients in SOLO-2 increased creatinine (11%), MDS/AML (8%), edema (8%), rash (6%), and lymphopenia (1%). Patients receiving Lynparza were neutropenia (19%), cough (18%), leukopenia (16%), and decreased platelets (15%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in SOLO-2.

Table 6 Adverse Reactions in SOLO-2 (% of Patients Who Received Lynparza)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza capsules n=195</th>
<th>Placebo n=99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grades 1-4 (%)</td>
<td>Grades 1-4 (%)</td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>79</td>
<td>13</td>
</tr>
<tr>
<td>Increase in hemoglobin</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>Decrease in creatinine</td>
<td>91</td>
<td>16</td>
</tr>
<tr>
<td>Decrease in leukocytes</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Decrease in platelets</td>
<td>35</td>
<td>24</td>
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*Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

The following adverse reactions and laboratory abnormalities have been identified in <10% of the 223 patients receiving Lynparza (table 9).

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<td>53</td>
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* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions observed in SOLO-2 that occurred in >20% of patients receiving Lynparza were nausea (49%), vomiting (43%), diarrhea (33%), headache (28%), and fatigue (25%). Discontinuation due to an adverse reaction occurred in 11% of patients receiving Lynparza.

Table 10 Laboratory Abnormalities Reported in Pooled Data

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Delivering the New Digital Patient Experience

by MEDICAL ECONOMICS® STAFF

TODAY’S PATIENT IS A true consumer of health care who expects convenience and efficiency. The COVID-19 pandemic rapidly accelerated patient expectations, thanks to the proliferation of telehealth and the use of online tools. Now that patients have seen how technology can improve their health care experience, practices must use the latest tools or risk losing patients to competitors.

A survey of patients conducted by PatientPop showed that 66% of respondents preferred a telehealth appointment over a traditional in-office visit. These individuals did not want to waste time in waiting rooms filling out paper forms; instead, they wanted the convenience of online forms and notifications about scheduling. By looking at successful practices, it is possible to determine a winning strategy.

During a panel discussion at the Medical Economics® 2021 Physician Bootcamp, Luke Kervin, cofounder and co-CEO of PatientPop, and Norm Schrager, the company’s head of content strategy, discussed the importance of adapting to new technological offerings.

Kervin and Schrager said patients are frustrated by inconsistency in how they connect with physicians outside the examination room and are unsure of the best way to communicate. This can lead to breakdowns in care or patients choosing different doctors. The most successful practices find ways to make the process easier for patients, whether it be in scheduling appointments or asking questions about treatment.

“Health care is one of the last major industries to be transformed by technology,” Kervin said. “Although electronic health records are well known to [those in practices], they are relatively invisible to patients and provide none of the consumer-oriented conveniences patients want from their doctors.”

Kervin said today’s patients want to schedule appointments online and have an open line of communication with the doctor’s office via text message or email. Practices that fail to provide these conveniences risk being left behind in health care’s competitive landscape.

Schrager said the patient experience has changed permanently. “The pandemic and the resulting shutdowns forced practices to adopt new technology [such as] telehealth at a rapid rate. Now that patients have seen telehealth improve their overall health care experience, there’s no going back. By the end of 2020, two-thirds of patients said they would prefer a telehealth visit in the future. The positive patient experience rating was going up for telehealth the more [that individuals] said they had virtual visits. I think this is a clear sign of the comfort that [individuals] have with any online or digital environment.”

Schrager also said patients prefer self-service, and practices need such functionality for tasks like scheduling appointments. A bonus, he added, is that patients who self-schedule are less likely to not show, be late, or cancel and are more likely to engage with their health and their physician.

Kervin and Schrager said preregistration intake forms need to be provided digitally and in advance; automated appointment reminders need to be sent via text message or email; and practices need to set up ongoing communication with each patient that starts when they land on the website and continues through every aspect of care.

Kervin noted that two-thirds of patients prefer text reminders, with another 15% opting for email.

“This is an open book for patient retention—for follow-up visits,” Kervin said. “[Patients] are actually telling [physicians], ‘Please send me a note when it’s time for me to book my next appointment,’ and they’re telling [the physicians how they prefer it sent].”

The technology benefits are not limited to existing patients, they explained. By adding online scheduling to the website, a practice can capture more business.

According to PatientPop, when a patient lands on a website that offers online scheduling, 51% of patients book online vs calling the practice, 66% of these appointments are with new patients, and 36% of the time they are scheduled after office hours.

“If you use online scheduling, last-minute cancellations create open slots that become available immediately for other patients to schedule at the last minute,” Kervin said.

As a result, no-show rates in the 15% range can drop to 4% to 5%, he added.

Kervin explained that online scheduling has become a major differentiator among practices; survey results showed that 63% of patients are more likely to choose one that offers it over one that does not.

When physicians add a well-designed website that highlights their practice’s strengths and manages their online reputation by asking for feedback, they can gain digital exposure and convert that traffic into scheduled appointments.

Kervin and Schrager concluded that by providing these technological conveniences, patients can be engaged in a way that helps them stay healthy and boosts a practice’s bottom line.

“Just be consistent [and] provide the patient a good experience that you know that they will respond to,” Schrager said.

To read the full article, visit Medical Economics®:
bit.ly/3DgeARv

51% of patients book online vs calling the practice

66% of these appointments are with NEW PATIENTS

36% of appointments are scheduled after hours when the practice is closed
WHO BETTER THAN NEW JERSEY’S PREMIER CANCER PROGRAM

RANKED BEST CANCER CENTER IN NEW JERSEY BY U.S. NEWS & WORLD REPORT
PART OF THE NCI-DESIGNATED GEORGETOWN LOMBARDI COMPREHENSIVE CANCER CENTER
ACCESS TO NOVEL THERAPIES WITH OVER 450 CLINICAL TRIALS
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When it comes to your cancer, there’s no question. New Jersey’s premier cancer program is Hackensack Meridian John Theurer Cancer Center.

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Overcoming Barriers to Clinical Access in Oncology Care Delivery Requires Multilevel Interventions

by CHRISTOPHER S. LATHAN, MD, MS, MPH

THE EFFECTS OF COVID-19 on our communities revealed the broken safety net of the health care system as images of men and women of color who needlessly lost their lives because of systemic racism flooded our screens and airwaves. Clinicians had been resistant in the past to overtly name systemic racism and classism, choosing instead to talk broadly about the social determinants of health.

Now, the entire cancer community is focused on going beyond descriptive research to consider real effect in broadening access to cancer care for our historically marginalized communities. There are many barriers to remove, but this discussion will focus on the Achilles’ heel of oncology: the lack of dissemination and implementation of evidence-based health care delivery innovations focused on addressing disparities in care. Although this issue is relevant to all cancer treatment sites, the problem starts with the National Cancer Institute (NCI)–designated centers, which have the noble task of improving cancer care via discovery and innovation.

MAGNIFYING AREAS OF IMPROVEMENT

Historically, many NCI-designated cancer centers have not been able to meet the needs of underserved communities effectively, given the scope and effect of their cancer center-based research despite years of discussion and good faith efforts by many individuals. As we now are fully aware of the effect of institutional barriers and systemic racism, we understand there has to be an integrated effort to achieve the treatment equity goal (FIGURE 1). There must be a focus on clinical access for underserved patients and it must be embedded as part of the clinical and operational flow of the cancer center. Although the national dialogue on this has been extraordinary, discussions centering on changes in the clinical delivery system have lagged considerably and it has become apparent that many clinical academicians are not aware of the established literature regarding interventions.

Many leaders in oncology systems are unfamiliar with program evaluation literature, have poor access to their own clinical data, and lack familiarity and respect for the decades of innovation and work that has been done to address disparities in cancer care. Leaders want quick fixes for a complex problem and do not appreciate being told that multilevel interventions are the best way to address the access issues. Community work is often separate from the both the operations of the cancer center and the majority of the basic, translational, and clinical trials research (FIGURE 2). It is no wonder that many institutions are reinventing the wheel as they try desperately to improve access to cancer care that closes disparity gaps in a demonstrable way.

STEPS TO IMPLEMENT CHANGE

There is evidence in results of investigative efforts that can give us some promising tools. The map has been laid out before us and central to any plan to improve clinical access for the marginalized community is the use of navigation as described by Harold P. Freeman, MD. The model he developed and published decades ago is an integral part of 3 cancer-specific interventions:

1. The work of the Delaware Cancer Consortium;
2. Findings presented by Robert H. Vonderheide, MD, DPhil, at the 2021 American Society of Clinical Oncology Annual Meeting on an intervention to increase access to the University of Pennsylvania’s cancer system; and
3. Findings presented and published by Cykert et al on an intervention to decrease disparities in lung cancer surgery.

The Delaware Cancer Consortium

The work of the Delaware Cancer Consortium was initially focused on eliminating disparities in colorectal cancer care.
in the state. Using a multilevel approach, the consortium expanded access to care to uninsured patients, integrated a centralized navigation process, and deepened relationships with community leaders, community health centers, and federally qualified health centers. The results of the efforts showed that the consortium not only eliminated the Black/White disparities in screening, but also narrowed survival differences. These findings have been available yet it is hardly mentioned as a model for expanding access and having relevant clinical effect on cancer outcomes. If these were the findings of a specific cancer therapeutic, its use would have spread far and wide by now.

“Leaders want quick fixes for a complex problem and do not appreciate being told that multilevel interventions are the best way to address access issues.”

— CHRISTOPHER S. LATHAN, MD, MS, MPH

**NEXT STEPS**

It is important to note that this is not an exhaustive list of interventions and that they are methodologically distinct. Despite the differences, they are all multilevel interventions developed in collaboration with the community and incorporate patient navigation into the methods.

If we are to move beyond talking about how best to reduce health care disparities and access in cancer care, we need to recognize that the work must be truly transdisciplinary and will require clinicians to recognize and respect a different literature. We must understand that this work is iterative and will require institutions to invest in clinical datasets as well as employ data analysts to move the work. If we really care about improving clinical access, we must admit where we have fallen short and invest our time and resources accordingly. The time is now.

Lathan’s primary research interests are centered on the effects of race, class, and access to care in cancer outcomes, including racial disparities in lung cancer treatment, differences in access to precision medicine by race and social class, and equitable distribution of new treatment across vulnerable populations. Lathan aims to bridge the gap between research efforts in disparities and the realities of patient care by developing interventions to increase access to high quality care, developed in part through community engagement. He remains a clinical oncologist focusing on lung cancer patients and is the founding director of the Cancer Care Equity Program at the Dana-Farber Cancer Institute, a clinical outreach program that aids in the diagnosis and treatment of cancer for patients at Federally Qualified Health Centers. His research interest focuses on leading systemwide efforts to broaden access to cancer care for historically marginalized groups to reduce disparities and improve health outcomes. Specific projects include (1) development of cancer-focused health equity measurement and data reporting tools; (2) patient navigation integration throughout the cancer service line; and (3) improving uptake of precision medicine in marginalized communities to advance cancer care.
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.1-10

Until RYBREVANT™—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.11

INDICATION
RYBREVANT™ (amivantamab-vmjw) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Infusion-Related Reactions
RYBREVANT™ can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT™. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT™ due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT™ as recommended. Administer RYBREVANT™ via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT™ infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT™ based on severity.

Interstitial Lung Disease/Pneumonitis
RYBREVANT™ can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT™, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT™ due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT™ in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions
RYBREVANT™ can cause rash (including dermatitis acniform, pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT™, including Grade 3 rash in 3.5% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT™ was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT™.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT™. Advise patients to wear protective clothing and use broad-spectrum UVU/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.
In a multicenter, open-label, multicohort study 10*

Results for tough-to-treat disease

40%
95% CI: 29%, 51%
(n=81)

3.7% of patients achieved a CR
36% of patients achieved a PR

Efficacy was evaluated by ORR and DOR 11

*ORR

MEDIAN DOR WAS 11.1 MONTHS 11

(95% CI: 6.9, NE 11)

The safety of RYBREVENT® was evaluated in the CHRYSALIS® study (n=129) 10:

- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity 10
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and increased sodium (4%).

Based on the safety population, N=302.

The innovation you’ve been waiting for.

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References:
RYBREVANT (amivantamab-vmjw) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in Full Prescribing Information], whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population [see Adverse Reactions], IRR occurred in 68% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 82% and 13% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended [see Dosage and Administration (2.3) in Full Prescribing Information]. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 [see Dosage and Administration (2.6) in Full Prescribing Information].

Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiac pulmonary resuscitation equipment and medication are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Intestinal Lung Disease/Pneumonitis
RYBREVANT can cause intestinal lung disease (ILD)/pneumonitis. Based on the safety population [see Adverse Reactions], ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (2.4) in Full Prescribing Information].

Dermatologic Adverse Reactions
RYBREVANT can cause rash (including dermatitis acuminata), pruritus, and dry skin. Based on the safety population [see Adverse Reactions], rash occurred in 74% of patients treated with RYBREVANT, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients [see Adverse Reactions].

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Ocular Toxicity
RYBREVANT can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population [see Adverse Reactions], keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1–2. Promptly refer patients presenting with new symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity [see Dosage and Administration (2.4) in Full Prescribing Information].

Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impaired embryofetal development, embryolethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT [see Use in Specific Populations].

ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions [see Warnings and Precautions]
- Intestinal Lung Disease/Pneumonitis [see Warnings and Precautions]
- Dermatologic Adverse Reactions [see Warnings and Precautions]
- Ocular Toxicity [see Warnings and Precautions]

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

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC who received a dose of 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) for at least 4 weeks, then every 2 weeks thereafter. Among 302 patients who received RYBREVANT, 97% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting, and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase.

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC who received RYBREVANT for at least 20 insertions mutations whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 38 to 84 years); 61% were female; 55% were Asian, 35% were White, and 23% were Black; and 82% had baseline body weight <80 kg. Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 73% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 95% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash and paronychia.

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.
Table 1: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSLAS.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>RYBREVANT (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>84</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>64</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
</tr>
<tr>
<td>Edema</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>47</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>37</td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>15</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
</tr>
</tbody>
</table>

* Rash: acne, dermatitis, dermatitis acerneiform, eczema, eczema stetic, palmar-planter erythodysesthesia syndrome, perineal rash, rash, rash erythematosus, rash maculo-papula, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis
* Fatigue: asthenia, fatigue
* Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling
* Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, and pulmonary sepsis
* Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
* Dyspnea: dyspnea, dyspnea exertional
* Cough: cough, productive cough, upper airway cough syndrome
* Stomatitis: aphthous ulcer, chelitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis
* Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort
* Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage
* Peripheral neuropathy: hypoaesthesia, neuralgia, paresthesia, peripheral sensory neuropathy
* Headache: headache, migraine

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, Ildpneumonitis, and toxic epidermal necrolysis (TEN).

Table 2: Select Laboratory Abnormalities ( ≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSLAS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYBREVANT+ (N=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Decreased album</td>
<td>79</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>53</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>38</td>
</tr>
<tr>
<td>Decreased phosphate</td>
<td>33</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>33</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>27</td>
</tr>
<tr>
<td>Increased gamma-glutamyl transferase</td>
<td>27</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>26</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>36</td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 128 based on the number of patients with a baseline value and at least one post-treatment value.

Immuneogenicity
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 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 amivantamab products may be misleading.

In CHRYSLAS, 3 of the 286 (1%) patients who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab-vmjw antibodies (one at 27 days, one at 59 days and one at 168 days after the first dose) with titers of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVANT.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy, Disruption or depletion of EGFR in animal models resulted in impairment of embryofetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and post-natal death in animals (see Data).

Advising pregnant women of the potential risk to a fetus.

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

Data
Animal Data
No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placentation, development, and embryo-fetal/prenatal survival and development.

Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/mice exposed to disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in
multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmiw has the potential to be transmitted from the mother to the developing fetus.

Lactation

Risk Summary

There are no data on the presence of amivantamab-vmiw in human milk or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose.

Females and Males of Reproductive Potential

RYBREVANT can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations].

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT.

Pediatric Use

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Geriatric Use

Of the 129 patients treated with RYBREVANT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions [see Warnings and Precautions].

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms [see Warnings and Precautions].

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT [see Warnings and Precautions]. Advise patients to apply alcohol free emollient cream to dry skin.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated [see Warnings and Precautions].

Paronychia

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia [see Adverse Reactions].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. [see Warnings and Precautions, Use in Specific Populations].

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose [see Use in Specific Populations].

Product of Ireland

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cp-213278v1
Higher Oncotype DX Scores Predict for Improved Endocrine Therapy Adherence in ER+ Breast Cancer

by TONY BERBERABE, MPH

HIGHER ONCOTYPE DX RECURRENCE scores were associated with prolonged persistence to 5 years of endocrine therapy vs lower Oncotype DX recurrence scores in patients with low-risk, estrogen receptor (ER)-positive/progesterone receptor–positive breast cancer, according to findings from a retrospective review that were presented at the 2021 San Antonio Breast Cancer Symposium.1

“Our findings suggest that the Oncotype DX breast recurrence score may influence [a patient’s] persistence [in taking] endocrine therapy,” Jonathan Pirruccello, MD, lead author and resident at Dartmouth-Hitchcock medical center in Lebanon, New Hampshire, said during the presentation of data.

The investigators hypothesized that patients with higher Oncotype DX breast recurrent scores may have higher rates of persistence when compared to a similar cohort with lower recurrence scores. Further, the individual perception of risk of recurrence conveyed by the Oncotype DX breast recurrent score directly influences persistence with endocrine therapy. Nonpersistence to endocrine therapy represents a major unmet need in breast cancer care with about 1 in 3 women discontinuing endocrine therapy early.2

The study evaluated 194 patients with low-risk, ER-positive breast cancer for at least 5 years. An Oncotype DX score of less than 26 was defined as low risk.

Persistence was determined by chart review and defined as a minimum duration of 55 months on endocrine therapy. The average recurrence score was 15.2 in the persistent group (n = 145) compared with 13.7 in the nonpersistent group (n = 49; P = .086) and the rate of distant and local recurrence was determined for both groups. The investigators reported that the average recurrence risk was 10.1% in the persistent group and 9.2% in the nonpersistent group (P = .91). The recurrence rate for distant and contralateral/local disease was 2% in the persistent group and 18% in the nonpersistent group. When observing only the distant recurrence rate, the persistent group had a recurrence rate of 0.6% compared with 10% in the nonpersistent group.

Recurrence rates were also lower for contralateral/local disease in the persistent group (1.3%) vs the nonpersistent group (8%). Further, rates of distant and contralateral/local disease recurrence were 2% vs 18%, respectively, and distant recurrence rates were 0.6% vs 10%.

Metastatic disease recurrence in women with low-risk, ER-positive breast cancer is due primarily to nonpersistence with endocrine therapy, according to investigators. There were 6 cases of metastatic breast cancer recurrence in a 5-to-8-year follow-up period, with 84% (5 of 6) of distant recurrences reported in the nonpersistent group, according to investigators.

“This finding further substantiates the overall effectiveness of endocrine therapy in reducing the risk of future recurrence in patients with low-risk, ER-positive breast cancer,” Pirruccello said. The findings suggest that most early metastatic recurrences in women with low-risk breast cancer may occur due to failure to complete the recommended 5-year course of therapy.

“Mindful framing of Oncotype DX test results by providers may present opportunities to increase persistence,” he continued.

The investigators recommended additional data collection to complete a total of 10-years follow-up to determine a recurrence rate that follows literature standards. They further recommended that any future interventions aimed at improving persistence should consider the effect of risk perception, particularly for those with lower Oncotype DX scores.

Oncotype DX is an assay that uses a 21-gene panel to estimate 10-year risk of recurrence in patients with ER-positive breast cancer undergoing endocrine therapy. The assay generates a recurrence score for each tumor sample, based on expression levels of 16 breast cancer–related genes normalized to 5 reference genes.3 An important risk factor for recurrence is nonpersistence or early discontinuation of endocrine therapy.

For a full list of references, see the article at OneLive.com.

Does a higher low-risk Oncotype DX recurrence score and associated risk of recurrence risk influence persistence to endocrine therapy?

<table>
<thead>
<tr>
<th>Persistent (n = 145)</th>
<th>Nonpersistent (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant and contralateral/local recurrence</td>
<td>98%</td>
</tr>
<tr>
<td>Contralateral/local recurrence</td>
<td>2%</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>1.3%</td>
</tr>
<tr>
<td>No recurrence</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

TOP TAKEAWAYS

- Findings suggest that a majority of early metastatic recurrences in patients with low-risk breast cancer may occur because of failure to complete the recommended 5-year course of endocrine therapy.
- Persistence with endocrine therapy depends in part on individualized perception of risk.
- The Oncotype DX test, and patient interpretation of the results, may influence long-term persistence to endocrine therapy.
- Mindful framing of results by providers may present opportunities to increase persistence.

A Determination to Improve Care Propelled a Targeted Therapy Pioneer

**Take a Prognosis of 3 Years, multiply it by 10, and what do you get? A staggering improvement in the survival of patients with chronic myeloid leukemia (CML) and a crucial stepping-stone on the road to targeted therapies for the treatment of a broad range of malignancies.**

Brian J. Druker, MD, director of the Knight Cancer Institute at Oregon Health & Science University (OHSU) in Portland, was the driving force behind those accomplishments when, in May 2001, his research led to the FDA's approval of imatinib (Gleevec). The oral tyrosine kinase inhibitor (TKI) initially indicated for patients with CML has proved to be one of the earliest and most successful targeted therapies in the oncology armamentarium.

By 2013, when Druker became a member of the inaugural Giants of Cancer Care® class, he noted that patients with CML who were taking imatinib were projected to survive an average of 30 years, a far cry from the 3- to 5-year prognosis that was standard when he began practicing medicine in the 1980s.

The prospects for this population continue to improve as a result of imatinib therapy and other novel TKIs introduced in the past 20 years. In the United States, life expectancy for those who respond to imatinib monotherapy is now close to normal.1,2

Today, imatinib is approved for the treatment of patients with newly diagnosed Philadelphia chromosome-positive CML in chronic phase as well as for patients with disease progression after interferon-alpha therapy. Additionally, the drug carries indications for patients with several other hematologic malignancies and KIT (CD117)-positive gastrointestinal stromal tumors.3

On a broader scope, the insights that led to the development of imatinib have helped lay the groundwork for a new era of targeted therapies not only in CML but also in many other cancer types. For Druker, success of imatinib flowed from a desire to improve outcomes for patients that took hold early in his career.

“Taking care of patients [with cancer] was pretty trying,” Druker recalled. “As medical oncologists, we were treating patients with breast, lung, colorectal, and prostate cancers...
who had metastatic malignancies. We could help them live a little longer with chemotherapy, but that often made it worse, not better, and it cured very few.

“I’d always come into this with the view that chemotherapy seemed barbaric, so I had no desire to continue to treat patients that way,” he said. “I decided I was going to go into the lab and not come out until I had something better—that was my commitment.”

GETTING STARTED

Druker began testing imatinib in 1993 after joining OHSU. Previously, in a lab at Dana-Farber Cancer Institute in Boston, Massachusetts, he had worked with tyrosine kinases, developing an antibody that could detect the modification of tyrosine residues through the addition of a phosphate. These findings enabled investigators to zero in on the BCR-ABL fusion protein.

“I thought about what human diseases were caused by this family of enzymes, and CML was one of them,” Druker said. “It made sense to me to work on a disease where I had lab expertise, but also in which we someday may have been able to treat patients [with new approaches].”

With that in mind, Druker headed to OHSU to find a promising CML treatment that he could test for activity and then bring to patients in the clinic. To accomplish this, he needed to locate a company that had developed such a compound, one that inhibited CML cells without harming normal ones. Amazingly, Druker found what he needed with a single phone call to Nicholas B. Lydon, PhD, at the former Ciba-Geigy Corporation.

Lydon had previously called upon Druker and his colleagues at Dana-Farber for help in establishing a pipeline of TKIs. Now, Lydon “thought he had compounds worth my testing,” Druker recalled. “It was really lucky, but if that hadn’t worked, I didn’t plan to stop. I would have continued to call people until I found a company with the right compounds.”

PUSHING THROUGH BARRIERS

Druker tested compounds and found that one, known as STI571, looked especially promising. The compound moved through a battery of lab tests and was transformed from an intravenous to an oral formulation after a problem with blood clots in animal subjects. In 1997, Novartis—formed through the merger of Ciba-Geigy and Sandoz—was still testing the compound but was concerned about liver and bladder toxicity in dogs and rats.

“As an oncologist who gives extremely toxic chemotherapy drugs to patients, I didn’t think that should kill the development program,” Druker recalled. “I asked if they had talked to the FDA, and they said that they weren’t ready.”

So Druker did it himself. He called someone at the FDA, described the data he had compiled about STI571, and asked whether the drug sounded ready to move into the clinic. Druker was told that he and Novartis had compiled more information than most companies with drugs already in clinical trials and that the drug’s toxicity profile did not sound like a deal breaker. The company subsequently gave the green light to the first trials that Druker had ever led, and the phase 1 studies of imatinib amounted to a hole in one.

In a phase 1 study, Druker and colleagues found that imatinib therapy resulted in complete hematologic responses in 53 of 54 patients with interferon-alpha-resistant CML, a response rate rarely seen in cancer with a single agent. Fifty-one patients maintained complete responses after a year on the medication, and the therapy was generally well tolerated.6

Imatinib was groundbreaking not just because of those results, but also because of its mechanism of action. Although previously approved drugs interfered with proteins associated with cancers, imatinib was the first to directly turn off the signal of a protein known to cause a cancer.

Clinical findings immediately generated enthusiasm in the oncology community. Druker presented phase 1 results at the 41st Annual Meeting of the American Society of Hematology on December 3, 1999, to a standing-room-only crowd. “You could have heard a pin drop during my presentation, and there was pretty thunderous applause at the end,” Druker recalled. “That was unusual because the typical reaction to a phase 1 trial is, ‘That’s interesting, but it’s still pretty early—we’ll need more studies to confirm it.’ In this case, there was just this incredible validation and genuine enthusiasm.”

Imatinib was approved while phase 2 trials were still in progress and after an FDA review of less than 3 months, an all-time speed record.

REACHING NEW MILESTONES

Since the success of imatinib, Druker has been a prolific investigator into the genomic landscape of a range of hematologic malignancies. His work has helped elucidate the role of the T315I gatekeeper mutation in the BCR-ABL kinase domain, contributing to the development of ponatinib (Iclusig). The OHSU Knight Cancer Institute credits his scientific and medical achievements with helping to raise more than $1 billion in donation pledges.

In 2009, Druker received the Lasker–DeBakey Clinical Medical Research Award in recognition of his work with CML. He shared the award with Lydon, the pharmaceutical industry investigator who helped identify imatinib as a potential therapy, and Charles L. Sawyers, MD, of Memorial Sloan Kettering Cancer Center, a 2013 Giants of Cancer Care® award winner in the prostate cancer category.

Druker was in good company again in 2019 when he received the Sjöberg Prize from the Royal Swedish Academy of Sciences. He shared the $1 million prize with Dennis J. Slamon, MD, PhD, of UCLA, a 2014 Giants of Cancer Care® award winner in the breast cancer category.

REFERENCES


2013 Giants of Cancer Care® Inductees

- Bernard Fisher, MD
- Elizabeth H. Blackburn, PhD
- Everett E. Vokes, MD
- Thomas J. Lynch, Jr, MD
- Steven A. Rosenberg, MD
- Vincent T. DeVita, Jr, MD
- Charles L. Sawyers, MD
- Bert Vogelstein, MD
- Moses Judah Folkman, MD

*Died in October 2019.
*Inducted posthumously.

To learn more about Giants of Cancer Care® program and read more about the 2013 class, scan the QR code or visit bit.ly/3G1N9ej.
For your adult patients living with Lambert-Eaton myasthenic syndrome (LEMS).

IT’S TIME FOR A COMEBACK

Help your adult patients move forward with FIRDAPSE® (amifampridine), the only FDA-approved, evidence-based therapy for the treatment of LEMS in adults.

FIRDAPSE has been proven in clinical trials to significantly improve muscle strength and patient perception of well-being.¹

INDICATIONS AND USAGE:
FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

SELECTED IMPORTANT SAFETY INFORMATION
FIRDAPSE can cause seizures. Do not use FIRDAPSE in patients with a history of seizures, or with a hypersensitivity to amifampridine or another aminopyridine.

Please see Brief Summary of full Prescribing Information on the next page.


Visit www.FIRDAPSEHCP.com to learn more.
FRIDAPSE® (amifampridine) Tablets 10mg

FRIDAPSE® (amifampridine) tablets for oral use

Brief Summary of Full Prescribing Information for FRIDAPSE

Indications and Usage
FRIDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

Dosage and Administration

- The recommended starting dosage is 15 mg to 30 mg daily taken orally in divided doses (3 to 4 times daily).
- Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment, and in whom N-acetyltransferase 2 (NAT2) poor metabolizers
- Dosage can be increased by 5 mg daily every 3 to 4 days.
- Dosage is not to exceed a maximum of 80 mg daily.
- The maximum single dose is 20 mg.

Contraindications
FRIDAPSE is contraindicated in patients with:
- A history of seizures
- Hypersensitivity to amifampridine phosphate or another amino pyridine.

Warnings and Precautions

Seizures
FRIDAPSE can cause seizures. Seizures have been observed in patients without a history of seizures taking FRIDAPSE at the recommended doses, at various times after initiation of treatment, at an incidence of approximately 2%. Many of the patients were taking medications or had comorbid medical conditions that may have lowered the seizure threshold. Seizures may be dose-dependent. Consider discontinuation or dose-reduction of FRIDAPSE in patients who have a seizure while on treatment. FRIDAPSE is contraindicated in patients with a history of seizures.

Hypersensitivity
In clinical trials, hypersensitivity reactions and anaphylaxis associated with FRIDAPSE administration have not been reported. Anaphylaxis has been reported in patients taking another amino pyridine, therefore, it may occur with FRIDAPSE. If anaphylaxis occurs, administration of FRIDAPSE should be discontinued and appropriate therapy initiated.

Adverse Reactions
The following serious adverse reactions are described elsewhere in the labeling:
- Seizures
- Hypersensitivity

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 clinical practice.

In controlled and uncontrolled trials (Study 1 and 2) in patients with LEMS, 63 patients were treated with FRIDAPSE, including 40 patients treated for more than 6 months, and 33 patients treated for more than 12 months. In an expanded access program 139 patients with LEMS were treated with FRIDAPSE, including 102 patients treated for more than 6 months, 77 patients treated for more than 12 months, and 53 patients treated for more than 18 months.

Study 1 was a double-blind, placebo-controlled, randomized discontinuation study in adults with LEMS. Following an initial open-label run-in phase (up to 90 days), patients were randomized to either continue FRIDAPSE treatment or transition to placebo for a 14-day double-blind phase. Following final assessments, patients were allowed to resume FRIDAPSE treatment for up to 2 years (open-label, long-term safety phase of the study).

During the open-label run-in phase of Study 1, 53 patients received FRIDAPSE for an average of 81 days at an average daily dosage of 50.5 mg/day. The average patient age was 52.1 years and 66% were female. There were 42 patients who had no prior exposure to FRIDAPSE at the initiation of this study.

Table 1 shows adverse reactions with an incidence of 5% or greater occurring in the 42 LEMS patients newly initiated on treatment with FRIDAPSE during the run-in phase of the study.

Table 1. Adverse Reactions in ≥5% of LEMS Patients Newly Treated with FRIDAPSE in Study 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>FRIDAPSE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasthesia†</td>
<td>62</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>33</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td>Elevated liver enzymes**</td>
<td>14</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>12</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>10</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10</td>
</tr>
<tr>
<td>Cataract</td>
<td>10</td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Bruxism</td>
<td>7</td>
</tr>
<tr>
<td>Fall</td>
<td>7</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>7</td>
</tr>
</tbody>
</table>

†Includes paraesthesia, palmar/plantar paraesthesia, paresthesia, peripheral paresthesia, paresthesia oral, and paresthesia genital.

**Includes elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT).

Other Adverse Reactions
In the overall population treated in Study 1 (n=53), including the double-blind phase and the 2-year open-label long-term safety phase, additional adverse reactions occurring in at least 5% of the patients included: dyspnea, urinary tract infection, gastroesophageal reflux, insomnia, peripheral edema, pyrexia, viral infection, blood creatine phosphokinase increase, depression, erythrocytosis, and influenza. These patients received an average daily dosage of 66 mg of FRIDAPSE.

Drug Interactions

Drugs that Lower Seizure Threshold
The concomitant use of FRIDAPSE and drugs that lower seizure threshold may lead to an increased risk of seizures. The decision to administer FRIDAPSE concomitantly with drugs that lower the seizure threshold should be carefully considered in light of the benefit and the risk of the associated risks.

Drugs with Cholinergic Effects
The concomitant use of FRIDAPSE and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of FRIDAPSE and of those drugs and increase the risk of adverse reactions.

Use in Specific Populations

Pregnancy
FRIDAPSE Pregnancy Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FRIDAPSE during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women who may register themselves in the registry by calling 855-212-5856 (toll-free), using the fax number 877-867-1874 (toll-free), by contacting the Pregnancy Coordinating Center at firdapsepregnancyregistry@ubc.com or by visiting the study website at www.firdapsepregnancystudy.com.

Risk Summary
There are no data on the developmental risk associated with the use of FRIDAPSE in pregnant women. Oral administration of amifampridine phosphate to rats during pregnancy and lactation resulted in developmental toxicity (increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development) at doses associated with maternal plasma drug levels lower than therapeutic drug levels (see Animal Data). In the U.S. general population, the estimated background risk may vary from birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Animal Data

Oral administration of amifampridine phosphate (0.75, 22.5, or 75 mg/kg/day) to female rats prior to and during mating and continuing throughout organogenesis produced no adverse effects on embryotrophic development. Plasma amifampridine exposure (AUC) at the highest dose tested is approximately 7 times that in humans at the maximum recommended human dose (MRHD) of 80 mg amifampridine/day. Oral administration of amifampridine phosphate (0.9, 30, or 57 mg/kg/day) to pregnant rabbits throughout organogenesis produced no adverse effects on embryotrophic development. The highest dose tested is approximately 7 times the MRHD (80 mg/day) amifampridine) on a body surface area (mg/m²) basis.

Oral administration of amifampridine phosphate (0.75, 22.5, or 75 mg/kg/day) to female rats throughout pregnancy and lactation resulted in an increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development in female pups at the mid and high doses tested. The no-effect dose (7.5 mg/kg/day amifampridine phosphate) for adverse developmental effects is associated with a plasma amifampridine exposure (AUC) less than that in humans at the MRHD.

Lactation
FRIDAPSE is excreted in human milk.

Risk of Seizures
There are no data on the presence of FRIDAPSE in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for FRIDAPSE and any potential adverse effects on the breastfed infant from FRIDAPSE or from the underlying maternal condition.

In lactating rats, amifampridine was excreted in milk and reached levels similar to those in maternal plasma.

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

Geriatric Use
Clinical studies of FRIDAPSE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not been established.

Drug Interactions
Instruct patients to notify their healthcare provider if they have signs or symptoms of hypersensitivity, and to seek emergency help if symptoms of anaphylaxis occur.

Pregnancy
Inform patients that FRIDAPSE can cause seizures, and to notify their healthcare provider if they experience a seizure.

Hypersensitivity
Instruct patients to inform their healthcare provider if they have signs or symptoms of hypersensitivity, and to seek emergency help if symptoms of anaphylaxis occur.

FRIDAPSE Dosage
Instruct patients to take FRIDAPSE exactly as prescribed. Patients should carefully follow the dose escalation schedule provided by their healthcare provider to safely achieve the therapeutic dosage. Inform patients that the tablets may be divided in half at the score, if needed. Instruct patients not to take a double dose to make up for a missed dose.

Drug Interactions
Instruct patients to notify their healthcare provider prior to starting any new medication, including over-the-counter drugs.

Pregnancy
Inform patients that if they are pregnant or plan to become pregnant while taking FRIDAPSE they should inform their healthcare provider. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to FRIDAPSE during pregnancy and encourage them to enroll if they become pregnant while taking FRIDAPSE. [See Use in Specific Populations (8.1) of Full Prescribing Information].

Storage
Advisory patients to store FRIDAPSE at 68°F to 77°F (20°C to 25°C).

Catalyst Pharmaceuticals

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Next Steps for KRAS Inhibitors Focus on Tackling Resistance

by JANE DE LARTIGUE, PhD

THE RECENT APPROVAL OF sotorasib (Lumakras) for the treatment of patients with advanced KRAS G12C-mutant non–small cell lung cancer (NSCLC) marks a milestone for cancer therapy. After 4 decades of research into the oncogenic implications of KRAS mutations in human cancers, the FDA’s May 2021 accelerated approval of the KRAS G12C inhibitor represents the first successful therapy directed at a target long considered undruggable.1,2

Having finally made some headway in 1 cohort of patients, investigators are focused on finding ways to broaden the impact of KRAS inhibition. They are describing mechanisms of resistance to these drugs and offering a number of potential paths forward, including exploring coinhibitory targets (FIGURE).3-7

Many mechanisms of resistance hinge on reactivation of the RAS/MAPK pathway. Combinations of KRAS G12C inhibitors with drugs targeting upstream and downstream components of related signaling networks are showing promise in NSCLC and colorectal cancer (CRC).8-11 Novel drug designs, such as RAS(ON) inhibitors, which target the active form of KRAS, could help tackle particularly challenging acquired resistance mutations that drive cross-resistance to KRAS G12C inhibitors.12

This year is shaping up to a busy one for KRAS research. Mirati Therapeutics’ adagrasib (MRTX849) is hot on the heels of sotorasib. The company expects to file a new drug application for the agent as a second-line treatment of patients with KRAS G12C–mutant NSCLC.13 A number of other companies are developing KRAS G12C inhibitors and vying for potential best-in-class status.14,15 These drugs are being tested as monotherapy and in combination with a range of targeted therapies in KRAS G12C–mutant solid tumors (TABLE). Amgen is continuing its development of trend-setting sotorasib, notably in the CodeBreaK 101 trial (NCT04185883), a master protocol that currently includes 15 substudies. Investigators aim to recruit more than 1000 participants with KRAS G12C-mutant advanced solid tumors, NSCLC, or CRC.

Meanwhile, clinical testing is expected to start on the first KRAS(ON) agent and on drugs targeting other KRAS variants that are more common in malignancies other than NSCLC.

RESISTANCE MECHANISMS

Although KRAS G12C inhibitors offer an important new therapeutic option for a subset of patients with NSCLC, clinical trial experience suggests that fewer than half of patients respond and responses can be short-lived.16,17 Furthermore, these drugs have modest activity as single agents in patients with CRC.3 In the phase 2 CodeBreaK 100 trial (NCT03600883), sotorasib monotherapy demonstrated an objective response rate (ORR) of 9.7% in 6 of 62 patients, all partial responses (PRs), according to peer-reviewing findings detailed in Lancet Oncology in December 2021. At the European
Society for Medical Oncology (ESMO) Congress 2021, investigators reported that adagrasib monotherapy resulted in a 22% response rate, including 1 unconfirmed PR, among 45 patients treated during the phase 1/2 KRYS TAL-1 (NCT03782549) study.2,10

Even preclinical studies have shown indications of variable degrees of sensitivity to KRAS G12C inhibitors, although it remains an open question whether this is mediated by activation of alternative wild-type KRAS proteins (NRAS and HRAS). Production of mutant KRAS G12C in the active guanosine triphosphate-bound state, or both.2,3,11,21

In nonmutant cells, KRAS is maintained in the active state (which is not targetable by current KRAS G12C inhibitors) by the activity of upstream receptor tyrosine kinases (RTKs) and SHP2, a phosphatase that activates RAS signaling downstream of multiple RTKs.21,22 Coinhibition of these targets may enhance the activity of KRAS G12C inhibitors.

Potential mechanisms of acquired resistance to KRAS G12C inhibitors were outlined by Pasi A. Jänne, MD, PhD, at the American Association for Cancer Research-National Cancer Institute-European Organisation for Research and Treatment of Cancer (AACR-NCI-EORTC) Virtual International Conference on Molecular Targets and Cancer Therapeutics in October 2021. Jänne, the 2021 Giants of Cancer Care® award winner in the lung cancer category, is director of the Lowe Center for Thoracic Oncology, the Belfer Center for Applied Cancer Science, and the Chen-Huang Center for EGFR Mutant Lung Cancers at Dana-Farber Cancer Institute in Boston, Massachusetts.24

During his presentation, Jänne noted that investigators are just beginning to understand these processes, with much of what is known having emerged over only the past several months.24

He highlighted 2 key studies. In the first, investigators conducted molecular analyses of tumor tissue and circulating tumor DNA from plasma samples from 38 patients (27 with NSCLC, 10 with CRC, and 1 with cancer of the appendix) who exhibited acquired resistance following treatment with adagrasib in the KRYS TAL-1 study.4

A potential underlying cause of resistance was identified in 17 of the 38 patients. Seven of these patients displayed multiple concurrent mechanisms of resistance, which appeared to be more common in patients with CRC. Secondary alterations of the KRAS gene were identified in 9 of the 17 patients and included G12D/R/V/W, G61H, R68S, H95D/Q/R, and Y96C mutations in addition to amplification of the KRAS G12C allele.4 Molecular alterations in non-KRAS genes involved in other RTK/RAS/MAPK signaling pathways were observed in 12 of the 17 patients and included activating mutations in NRAS, BRAF, MAP2K1, and RET; gene fusions involving ALK, RET, BRAF, RAF1, and FGFR3; and loss-of-function mutations in NFI and PTPN1. Transformation from adenocarcinoma to squamous cell histology also was observed in 2 patients with NSCLC.4

In the second study, investigators used the chemical mutagen N-ethyl-N-nitrosourea to induce mutations in the KRAS gene, transduce the mutated genes into cell lines, and then study their impact on KRAS G12C inhibitor activity.5 Among clones resistant to sotorasib (n = 68), 52 harbored secondary KRAS mutations, most commonly A59T, R68M, and Y96D following high doses (≥ 1000 nM) of the drug, and G13D, A59S, R68M, and G61L after lower doses (100nM-500 nM). Clones resistant to adagrasib (n = 74), 72 of which involved secondary KRAS mutations, most commonly harbored Y96D mutations after a high dose (≥ 200 nM) of adagrasib and O99L, R68S, V8E, M72I, and A59S variants after low doses (20-100 nM).6

Investigators also evaluated the degree of resistance associated with each KRAS mutation. G13D, A59S/T, R68M, and Y96D/S mutations were all identified as highly resistant to sotorasib, whereas Y96D/S and O99L conferred strong resistance to adagrasib. Some variants, such as V8E, G13D, A59S/T, and R68M that were resistant to sotorasib remained sensitive to adagrasib; the reverse was true for the O99L mutation, which was resistant to adagrasib but remained sensitive to sotorasib. Notably, the Y96D/S mutations were identified as a mechanism of cross-resistance to both KRAS G12C inhibitors.6

### TABLE. Select Clinical Trials of Combination Therapies in KRAS G12C-Mutant Solid Tumors

<table>
<thead>
<tr>
<th>KRAS G12C inhibitor (drug developer)</th>
<th>Combination regimens</th>
<th>Phase (ClinicalTrials.gov identifier)/tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotorasib (Lumakras) [Mirati Therapeutics]</td>
<td>+ AMG 404 or pembrolizumab (PD-1 inhibitor)</td>
<td>Phase 1b/2 CodeBreak 101 trial (NCT04185098) in advanced solid tumors, NSCLC, or CRC</td>
</tr>
<tr>
<td></td>
<td>+ Vemurafenib (MEK inhibitor)</td>
<td>Phase 1/2 RAMP203 trial (NCT05078410) in NSCLC</td>
</tr>
<tr>
<td></td>
<td>+ PD-0318406 (SHP2 inhibitor)</td>
<td>Phase 1b/2 RAMP203 trial (NCT05078410) in NSCLC</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>+ BI 1701963</td>
<td>Phase 1b/2 RAMP203 trial (NCT05078410) in NSCLC</td>
</tr>
<tr>
<td></td>
<td>+ VS-6766 (MEK/RAF inhibitor)</td>
<td>Phase 1b/2 RAMP203 trial (NCT05078410) in NSCLC</td>
</tr>
<tr>
<td>Adagrasib (MRTX849) [Mirati Therapeutics]</td>
<td>+ Cetuximab (EGFR inhibitor)</td>
<td>Phase 3 KRYS TAL-10 trial (NCT04793958) in CRC</td>
</tr>
<tr>
<td></td>
<td>+ Pembrolizumab + Afatinib + Cetuximab</td>
<td>Phase 1/2 KRYS TAL-1 trial (NCT03785244) in NSCLC, CRC</td>
</tr>
<tr>
<td></td>
<td>+ BI 1701963</td>
<td>Phase 1/2 CRYS TAL-1 trial (NCT03785244) in NSCLC, CRC</td>
</tr>
<tr>
<td></td>
<td>+ BI 1701963</td>
<td>Phase 1/2 RAMP203 trial (NCT05078410) in NSCLC</td>
</tr>
<tr>
<td>JQ443 (Novartis Pharmaceuticals)</td>
<td>+ Spartalizumab (PD-1 inhibitor)</td>
<td>Phase 1/2 study (NCT04499188) in advanced solid tumors</td>
</tr>
<tr>
<td>JAB-21622 (Jacobios Pharmaceuticals)</td>
<td>+ Cetuximab</td>
<td>Phase 1/2 study (NCT05002270) in CRC</td>
</tr>
<tr>
<td>BI 1823911 (Boehringer Ingelheim)</td>
<td>+ BI 1701963</td>
<td>Phase 1/2 study (NCT04973163) in solid tumors</td>
</tr>
<tr>
<td>GDC-6036 (Genentech)</td>
<td>+ GDC-1971 (SHP2 inhibitor) + Atazanavir</td>
<td>Phase 1 study (NCT04449874) in advanced solid tumors, NSCLC, CRC</td>
</tr>
<tr>
<td></td>
<td>+ Atazanavir + Cetuximab</td>
<td>Phase 1 study (NCT04449874) in advanced solid tumors, NSCLC, CRC</td>
</tr>
<tr>
<td></td>
<td>+ Bevacizumab</td>
<td>Phase 1 study (NCT04449874) in advanced solid tumors, NSCLC, CRC</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer.

*Trial includes 1 or more arms testing KRAS G12C inhibitor monotherapy.

*Trial is not yet recruiting participants.
**The Breakthrough: Novel Drug Design Cracks the KRAS Puzzle**

**by JANE DE LARTIGUE, Ph D**

UNTIL RECENTLY, THE KRAS PROTEIN, which was first linked to cancer in the 1980s, had stubbornly resisted all drug development efforts. KRAS functions as a molecular switch that toggles between inactive and active states by binding to guanosine diphosphate (GDP) or guanosine triphosphate (GTP), respectively.

The switch is tightly controlled by numerous associated proteins, including guanine nucleotide exchange factors, which stimulate the dissociation of GDP and subsequent association of GTP, and GTPase-activating proteins (GAPs) that boost the intrinsic GTPase activity of KRAS to catalyze the hydrolysis of GTP back to GDP.

KRAS integrates signals from receptor tyrosine kinases at the cell surface and transmits them downstream via a plethora of signaling pathways, most notably the MAPK pathway, ultimately mediating various cellular processes.

KRAS is an attractive therapeutic target because activating mutations in the KRAS gene are among the most common molecular alterations in cancer, particularly in pancreatic, colorectal cancer (CRC), and lung cancers. In general, the mutations render the KRAS protein resistant to GAP-mediated hydrolysis, tipping the balance in favor of activated KRAS, which promotes many of the hallmarks of cancer.

The majority of oncogenic KRAS mutations occur at hotspots within codons 12 (~82%) and 13 (~14%). The specific amino acid substitutions involved vary according to the type of cancer; in NSCLC, KRAS G12C predominates, whereas KRAS G12D is somewhat more common in pancreatic cancer and CRC.

In 2013, investigators identified a hidden pocket next to the mutant cysteine in the KRAS G12C protein that was only revealed in the GDP-bound form, which finally offered a direct drug-binding site. In May 2021, the FDA granted an accelerated approval to sotorasib (Lumakras), a first-in-class KRAS G12C inhibitor based on this drug design, for previously treated adult patients with KRAS G12C–mutant locally advanced or metastatic NSCLC.

Approval was based on results from the CodeBreak 100 study (NCT03600883), a multicenter, single-arm trial involving 124 efficacy-evaluable patients with KRAS G12C–mutant NSCLC. Over a median follow-up of 15.3 months (range, 1.1 to 18.4+), the confirmed ORR was 37.1% (95% CI, 28.8%-46.6%), including 4 complete responses.

Median progression-free survival was 6.8 months (95% CI, 5.1-8.2) and median overall survival was 12.5 months (95% CI, 10.0-not evaluable). Treatment-related adverse effects (TRAEs) of at least grade 3 occurred in 19.8% of patients, most commonly liver enzyme elevations. To identify the KRAS G12C mutation, the QIAGEN therascreen KRAS RQG PCR kit for testing tissue and the Guardant360 CDx assay for testing plasma were approved as companion diagnostics.

The phase 3 confirmatory CodeBreak 200 trial in NSCLC (NCT04303780), in which sotorasib is being compared against docetaxel in KRAS G12C–mutant NSCLC, is among ongoing clinical trials of sotorasib.

The FDA recently awarded a breakthrough designation to a second KRAS G12C inhibitor, adagrasib (MRTX849), for patients with KRAS G12C–mutant NSCLC following prior systemic therapy based on positive results from the KRYS-TAL-1 trial (NCT03785249). Among 51 efficacy-evaluable patients with KRAS G12C–mutant NSCLC treated with adagrasib, the ORR was 45%, all partial responses. The most common TRAEs included nausea, diarrhea, vomiting, fatigue, and increased alanine aminotransferase levels.

For a full list of references, see the article at OncLive.com

This illustration depicts the small molecule inhibitor sotorasib nestled in the binding pocket of the KRAS G12C (cysteine at position 12) protein. The orange molecule with the colored sticks at left shows the KRAS G12C protein bound to guanosine diphosphate in its inactive state and the purple section represents Switch II. The turquoise section creates a groove that enhances sotorasib’s binding and potency properties.

Image courtesy of Amgen.

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960 mg daily plus panitumumab 6 mg/kg every 2 weeks, including 5 participants previously treated with sotorasib. In this cohort of 8 patients, there was 1 confirmed PR and 5 patients experienced SD. In the dose-expansion phase (part 2 cohort A), results were reported for 18 patients who were naïve to KRAS G12C inhibitor therapy and received the sotorasib/panitumumab combination at the recommended dose. There were 3 confirmed and 3 unconfirmed PRs plus 12 participants with SDs, for a DCR of 83.3%. Among the 41 enrolled patients, there were no DLTs or grade 4 or higher TRAEs.6

In another presentation at the 2021 ESMO Congress, investigators described data from a cohort of patients with CRC receiving adagrasib in combination with the EGFR antibody cetuximab (Erbitux) in the KRYS TAL-1 study. Among the 28 patients evaluable for response, the ORR was 43% including 2 unconfirmed PRs and the DCR was 100%. Grade 3/4 TRAEs were reported in 16% of patients, but there were no fatal events.7 The phase 3 KRYS TAL-10 trial (NCT04793958) of this combination in KRAS G12C-mutant CRC is ongoing.

Given the apparent complexity of KRAS G12C inhibitor resistance, in which alterations in multiple different RTKs are implicated,4,22 the SHP2 protein, a central node in the RAS pathway that lies downstream of multiple different RTKs, has emerged as an attractive therapeutic target.2 A number of SHP2 inhibitors are in development, several of which are being evaluated in combination with KRAS G12C inhibitors. BBP-398, a SHP2 inhibitor, is being evaluated in a phase 1 trial (NCT04528836) as monotherapy in patients with advanced solid tumors harboring KRAS G12C mutations or MAPK pathway alterations, including BRAF V600X mutations.

**Tackling Cross-Resistance**

Findings from studies of the mechanisms of acquired resistance to KRAS G12C inhibitors suggest that switching between these inhibitors upon progression could be effective against some KRAS resistance mutations. On the other hand, the Y96D/S variants appear to mediate cross-resistance to both drugs and present a particular therapeutic challenge.6

In the preclinical setting, combining KRAS G12C inhibitors with an inhibitor of the guanine nucleotide exchange factor SOS1 or with a SHP2 inhibitor was found to be active against the Y96D/S mutant.4 Several ongoing clinical trials are evaluating the combination of the SOS1 inhibitor BI 1701963 with KRAS G12C inhibitors.

The Y96D mutation also was shown to be susceptible to a new type of KRAS inhibitor that targets the GTP-bound form of the protein. Steve Kelsey, MD, MB ChB, FRCPath, FRCPath, president of research and development at Revolution Medicines, which is developing these new drugs, described these KRAS(ON) inhibitors during a presentation at the 2021 AACR-NCI-EORTC conference.12

Based on the company’s proprietary tricomplex inhibitor technology, these drugs exploit cyclophilin A, a chaperone protein, to create a binding pocket for the RAS inhibitor on the smooth surface of the GTP-bound KRAS G12C protein. In addition, binding of the cyclophilin A protein to the active mutant protein blocks it from interacting with downstream effectors.12

A first-in-class KRAS G12C(ON) Inhibitor, RMC-6291, is in preclinical development. The agent demonstrated a superior response rate compared with adagrasib in NSCLC KRAS G12C xenografts with an ORR per mouse RECIST of 68% (13 of 19 xenografts) vs 42% (8 of 19 xenografts), respectively.12

**Beyond KRAS G12C**

Revolution Medicines also is using its tricomplex technology to develop RAS(ON) inhibitors that target all KRAS variants. Although these pan-RAS(ON) inhibitors also have activity against wild-type RAS isoforms, meaning that they are likely to cause more toxicity than KRAS G12C inhibitors, they may offer another strategy for overcoming resistance.12

Lead candidate RMC-6236 has demonstrated antitumor activity in G12D-, G12V-, and G12R-mutant preclinical models, with notable activity against variants implicated in resistance to KRAS G12C inhibitors, according to Kelsey. Revolution Medicines plans to advance both RMC-6291 and RMC-6263 into clinical trials.12

Meanwhile, Mirati Therapeutics is developing MRTX1133, a KRAS G12D inhibitor with high affinity for both the active and inactive forms of the KRAS G12D-mutant protein. MRTX1133 has demonstrated potent antitumor activity in KRAS G12D-mutant xenograft models, with tumor regression in 60% of models and response in 73% of pancreatic cancer and 25% of CRC models.25 Mirati expects to file an investigational new drug application for MRTX1133 in 2022.3

Jane de Lartigue, PhD, is a freelance medical writer based in Gainesville, Florida.

**Key References**

- Riley GJ, Ou SHI, Rybkin I, et al. KRYS TAL-1: activity and preliminary pharmacodynamic (PD) analysis of adagrasib (MRTX849) in patients (Pts) with advanced non–small cell lung cancer (NSCLC) harbor-
SIMBA Therapy Encounters Barriers But Holds Promise for Neutropenia and Beyond

by CHRISTINA T. LOGUIDICE

CYTOTOXIC CHEMOTHERAPY CAN CAUSE significant and sometimes prolonged neutropenia, often increasing the risk of hospitalization and life-threatening infections. To reduce the risk of these complications, which can lead to poor outcomes, prophylactic granulocyte colony-stimulating factors (G-CSFs) are used, but these agents can be burdensome to administer and have toxicities such as bone pain that can affect patients’ quality of life. A novel agent has emerged that shows promise in addressing these challenges: a selective immunomodulating microtubule-binding agent (SIMBA) called plinabulin. “Not only does it affect progenitors that can affect the blood counts, but it may also have an anticancer effect,” William J. Gradishar, MD, said during a recent OncLive Peer Exchange®.

Gradishar was joined by a panel of breast cancer experts who discussed plinabulin, including some promising data from several clinical trials, including the pivotal phase 3 PROTECTIVE-2 trial (NCT03294577). “It would be nice to give all the medication on the same day and have good control without worrying about a drug not working or how many doses of short-acting growth factor to give and when,” said Hope S. Rugo, MD, FASCO. Based on the positive data, plinabulin was under review with the FDA at the time of the Peer Exchange; however, the FDA recently issued a complete response letter (CRL) requesting an additional trial before the agent could be approved for chemotherapy-induced neutropenia (CIN).

In addition to reviewing plinabulin, the panelists briefly discussed several other novel chemoprotective therapies under exploration, including trilaciclib (Cosela), which was recently approved to reduce chemotherapy-induced bone marrow suppression in patients with extensive-stage small cell lung cancer (SCLC).

HURDLES DELAY APPROVAL OF PLINABULIN
On December 1, 2021, the FDA issued a CRL to BeyondSpring Pharmaceuticals’ new drug application (NDA) for approval of plinabulin in combination with G-CSF to prevent CIN. The CRL indicated that the results of PROTECTIVE-2 were “not sufficiently robust to demonstrate benefit and that a second well-controlled trial would be required to satisfy the substantial evidence requirement to support the CIN indication.” The rejection was surprising and it has been reported that it may have resulted from an early miscommunication between BeyondSpring and the FDA. Although the NDA focused on data from the phase 3 PROTECTIVE-2 trial, it also included data from 5 supportive trials that collectively enrolled over 1200 patients; however, the FDA considered only the phase 3 data and deemed it insufficient. In contrast, BeyondSpring anticipated that all included data would be considered.

In a news release announcing the FDA’s decision, BeyondSpring did not commit to a second...
study but said it “expects to work closely with the FDA to consider the possible future clinical pathway for CIN, which may include a second study.” Analysts anticipate that a meeting between BeyondSpring and the FDA will occur early next year. Discussions to file a new application for approval in non-small cell lung cancer (NSCLC) are also planned based on data from the DUBLIN-3 trial (NCT02504489).4,5

Mechanism of Action and Administration
Plinabulin is a SIMBA, which is a potent antigen-presenting cell inducer. “Not only is it capable of potentially preventing the deep neutropenia that we see in some patients, but it also may have an effect on the immune system,” Gradishar said. He explained that plinabulin binds to microtubules and releases the protein GEF-H1, activating the signaling pathway. Once that pathway is activated, there is a maturation of dendritic cells, which then present the antigen to the T cells, leading to their activation.

“Before we had the acronym SIMBA, we were focusing more on the properties that affected blood counts, specifically, the intensity and depth of neutropenia. In one of the clinical trials [it was] suggested that there was indeed an antitumor effect, which broaden the acronym to take that into account,” he said.

Because of plinabulin’s dual action in preventing neutropenia and potentially exerting antitumor effects, the panelists expressed interest in learning how this agent may interact with certain anticancer treatments down the road, particularly checkpoint inhibitors. “It’s so fascinating that a drug that’s been developed for neutropenia could also have other effects that could potentially affect the efficacy of the agents that we’re using by helping the immune system recognize tumor cells,” Rita Nanda, MD, said.

Plinabulin is given as a single dose per chemotherapy cycle via a 30-minute intravenous (IV) infusion. It is administered on the same day, 30 minutes after the chemotherapy dose.

Clinical Trials
The panelists’ discussion focused on 3 trials that evaluated plinabulin: the phase 2/3 PROTECTIVE-1 trial (NCT03102606),9 the pivotal phase 3 PROTECTIVE-2 trial,7 and the phase 3 DUBLIN-3 trial.5

PROTECTIVE-1
PROTECTIVE-1 is a global, multicenter, double-blind trial that randomly assigned 105 patients with breast, lung (NSCLC), or hormone-refractory prostate cancer 1:1 to receive 4 cycles of docetaxel 75 mg/m2 plus placebo on day 1 and pegfilgrastim 6 mg on day 2 (n = 52) or docetaxel 75 mg/m2 plus placebo on day 1 and pegfilgrastim 6 mg on day 2 (n = 52).2 “The small study was designed as a noninferiority trial to look at days of severe neutropenia, and built into the trial were almost daily CBCs [complete blood counts] and tracking of the neutrophil count,” Tiffany A. Traina, MD, said.

The study met its primary end point, with significantly fewer days of neutropenia in the plinabulin arm vs the pegfilgrastim arm. Severe neutropenia was defined as absolute neutrophil count of less than 0.5 cells × 109/L. The mean duration of severe neutropenia (DSN) in cycle 1 was 0.246 days in the pegfilgrastim arm (95% CI, 0.205-0.287), compared with 0.770 in the plinabulin arm (95% CI, 0.682-0.857).9 Several secondary end points also favored plinabulin (Table 1).

Traina said another advantage in the plinabulin arm was significantly less bone pain and less thrombocytopenia. “I don’t know if that was anticipated, but it was observed,” she added. Overall, plinabulin was well tolerated, with a comparable safety profile to pegfilgrastim. Trina noted that the most common adverse effects (AEs) included low-grade infusion reactions and gastrointestinal toxicity, including nausea, diarrhea, and fatigue. “It can be potentially hard to tease out what is related to docetaxel, given that both arms are receiving backbone chemotherapy, but it did appear well tolerated,” Trina said.

Nanda and Gradishar pointed out that the PROTECTIVE-1 study shows several benefits of single-agent plinabulin over single-agent pegfilgrastim. These include its ease of use and reduced risk of thrombocytopenia, which is another major concern with chemotherapy, particularly platinum agents, and a reduction in patients experiencing bone pain. “When we talk about effects of these drugs, we’re usually worried about the pleiotropic effect or the off-target effect,” Gradishar said. “What we’re describing here is a drug that is pretty well tolerated, easy to give, and the off-target effects are favorable for the patient regarding neutropenia and a potential antinecancer effect. Right now, it looks like a very favorable kind of drug to be using.”

PROTECTIVE-2
The PROTECTIVE-2 study assessed whether combining plinabulin with pegfilgrastim could be beneficial. “One rationale for putting these 2 agents together, plinabulin plus pegfilgrastim, would be more of the continuous protection against neutropenia throughout that intercycle duration,” Trina said. Data show that plinabulin mainly exerts its CIN preventive effects in week 1 of the cycle when more than 75% of clinical complications occur.4 In contrast, G-CSFs such as pegfilgrastim primarily exert their CIN-preventive effects during week 2 of the cycle.6 “We still get that [absolute neutrophil count] nadir, and then we get quicker recovery,” she said.

PROTECTIVE-2 is a global, multicenter, double-blind trial that randomly assigned 221 patients with ECOG scores of 0 or 1 who were receiving docetaxel 75 mg/m2, doxorubicin (50 mg/m2), and cyclophosphamide (500 mg/m2), a regimen known as TAC, to receive either plinabulin (40 mg) plus pegfilgrastim (6 mg) or pegfilgrastim (6 mg) plus placebo.6 “Lack of grade 4 neutropenia was the primary end point,” Trina said.

She noted that PROTECTIVE-2 met its primary end point. In data presented that the 2021 American Society of Clinical Oncology Annual Meeting, investigators showed that among the 110 patients in the plinabulin/pegfilgrastim arm 31.53% were protected from grade 4 neutropenia vs 13.64% of those treated with pegfilgrastim alone (n = 111) in cycle 1 (P = .0015). As in PROTECTIVE-1, several secondary end points were clinically meaningful. Febrile neutropenia was observed in 3.60% of patients treated with the combination vs 6.36% of patients treated with pegfilgrastim alone through cycle 4 (P = .36).

Additionally, when considering cases of profound neutropenia, measured as an absolute neutrophil count of 100 per μL, the combination treatment improved clinical benefit by close to 50%. The median duration of febrile neutropenia with the combination was 1.25 days, compared...
with 2,28 days with pegfilgrastim alone. The rates of hospitalization were 75% with the combination vs 100% with pegfilgrastim alone and the median duration of hospitalization was 3.75 days vs 7.14 days, respectively. The administration of plinabulin/pegfilgrastim resulted in 2.7% of patients adjusting the chemotherapy dose and/or regimen in later cycles, compared with 6.3% of patients who received pegfilgrastim alone.1

Traina said bone pain was also reduced with the combination. Patients who received the combination experienced bone pain at a frequency of 18%, compared with 30% among those who received pegfilgrastim alone (P = .03).2 “It’s certainly more comfortable for our patients,” Traina said.

Another exciting finding Traina highlighted was that overall incidence of grade 4 events was significantly lower in the combination arm. “Plinabulin plus pegfilgrastim had 20% lower grade 4 adverse events with TAC compared with TAC with pegfilgrastim. It seems to be having an effect beyond just affecting the neutrophil count,” she said.

Nanda said she has not used TAC in many years, noting that it is a challenging regimen for patients, making any agent that can help with tolerability welcomed. “I think an improvement in quality of life in addition to the reduction of AEs and chemotherapy-induced neutropenia and febrile neutropenia is a home run,” she said, adding that she is interested in seeing whether plinabulin may have benefit in the setting of other difficult-to-tolerate chemotherapy regimens, particularly those used in patients with early-stage triple-negative breast cancer.

**DUBLIN-3**

DUBLIN-3 is a phase 3, global, randomized, single-blind, active-controlled trial that included 559 patients with epidermal growth factor receptor wild type NSCLC with measurable lung lesions being treated in the second and third line. Patients were treated on a 21-day cycle with docetaxel 75 mg/m² on day 1 and plinabulin 30 mg/m² on days 1 and 8 or with docetaxel alone.3 Unlike PROTECTIVE-1 and PROTECTIVE-2, the primary end point was overall survival (OS).

The mean and median OS rates were significantly improved in the plinabulin arm (Table 2). Additionally, OS rates doubled with plinabulin/docetaxel vs docetaxel alone at 24 months (22.13% vs 12.51%; P = .0072), 36 months (11.73% vs 5.27%; P = .0393), and 48 months (10.6% vs 0%; P value not determinable). Secondary end points favoring plinabulin/docetaxel over docetaxel alone included investigator-assessed overall response rate (12.23% vs 6.76%, respectively; P = .0275) and mean progression-free survival (6.0 vs 4.4 months, respectively; P = .0062).4

“The differences that were presented were modest, but to see an agent that not only prevents neutropenia but also has anticancer properties is pretty exciting,” Nanda said. “It is certainly worthy of additional investigation, particularly as we’re moving immunotherapy into the early-stage setting.”

**OTHER NOVEL CHEMOPROTECTIVE AGENTS**

A variety of other agents are being explored as prophylaxis against CIN. One such agent, trilaciclib, received FDA approval on February 12, 2021, to reduce the frequency of CIN in patients with small cell lung cancer.5 Approval was based on data from 3 randomized phase 2 trials that showed that use of G-CSFs, erythropoiesis-stimulating agents (ESAs), and red blood cell (RBC) transfusions on or after week 5 was significantly lower among patients receiving trilaciclib vs placebo (28.5% vs 56.3%, P < .0001; 3.3% vs 11.8%, P = .0254; and 14.6% vs 26.1%, P = .0252, respectively).5 Additionally, when severe neutropenia occurred, the duration was reduced in patients who received trilaciclib.

The panelists noted that trilaciclib is also being explored for breast cancer. “It did not show the same [benefit in reducing neutropenia] in breast cancer with a different chemotherapy backbone,” Rugo said. “It’s intriguing that these drugs may work differently based on the kind of chemotherapy backbone we have as well.”

Although the primary end point of a reduction in grade 4 neutropenia was not met in the trial, Rugo mentioned that in results from an ongoing phase 2 trial (NCT02978716) assessing the addition of trilaciclib to gemcitabine/capcitabatin in women with triple-negative breast cancer, there was an unexpected positive finding.7 The investigators observed a 63% reduction in the risk of death (P < .0001) with the addition of trilaciclib.

“Other compounds are being investigated, including one that goes by the acronym ALRN-0924, which is a peptide that may also have

A similar effect on preventing neutropenia,” Gradishar said. A phase 1b trial (NCT04022876) is assessing ALRN-06924 in preventing chemotherapy-induced AEs in patients with small cell lung cancer or NSCLC treated with carboplatin/pemetrexed. The trial is currently recruiting patients.9

**REFERENCES**


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