Precision Era Biomarkers Get a Closer Look

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OncPathways
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WORLD GI CONFERENCE HIGHLIGHTS
Updates on Treatment Strategies for Unresectable HCC and BRAF V600–mutant CRC

THE TALK
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DRUG SPOTLIGHT
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By Lakshmi Hayak, MD
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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 46.
Circulating tumor DNA, tumor mutational burden, and homologous recombination deficiency represent 3 measurable biologic features driving innovative efforts to guide strategic therapeutic efforts for patients with cancer. Investigative initiatives under the leadership of Friends of Cancer Research are underway to develop a better understanding of these markers.

8 Precision Era Biomarkers
Get a Closer Look

by ANITA T. SHAFFER

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IN A WORLD FILLED WITH COVID-19...

CIN CAN STRIKE AT ANY MOMENT

It’s time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

TO LEARN MORE, VISIT CINRisk.com

With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer.

Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.1

When your patients are left unprotected, particularly in Cycle 1,2 CIN may lead to life-threatening events, such as fever, infection, and hospitalization3–severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.4-6

References:
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Liquid Biopsy Leads Next Era of Precision Medicine

AN INCREASED EMPHASIS ON leveraging information from biomarkers has led to breakthrough treatment options for patients with non–small cell lung cancer, colorectal cancer, prostate cancer, breast cancer, and more. As investigators navigate the utility of markers including circulating tumor DNA (ctDNA), tumor mutational burden (TMB), and homologous recombination deficiency (HRD), developers of companion diagnostic tools are looking to refine and capitalize on the expanding market.

A recent report detailing the forecast of the global liquid biopsy market anticipates growth exceeding more than US $3.0 billion by 2024 and reaching $8.2 billion by 2027. The report cites applications in oncology as one of the driving forces of growth with lung and breast cancer diagnostics accounting for the largest share of the liquid biopsy market.¹

Investigative efforts to unlock the utility of ctDNA, TMB, and HRD across tumor types are taking shape as clinical trials incorporate testing into study design and institutional efforts to explore recent data commence. For instance, Friends of Cancer Research has initiated the ctDNA for Monitoring Treatment Response (ctMoniTR) Project, which seeks to expand the potential of ctDNA as it relates to responses to therapy.²

In this month’s cover story, Mark Stewart, PhD, vice president of science policy at the Friends group said that biomarkers present an opportunity to improve clinical care in oncology as well as aid the future of drug development. “Developments over the past year and from the diagnostic market have really shown that these complex biomarkers are becoming increasingly used and important in oncology care,” Stewart said regarding TMB and HRD testing. “But with these complex biomarkers, we have to recognize that they’re complex for a reason.”

As the available technologies with varying levels of sensitivity are introduced, understanding their current applications and future directions, will lean on educational efforts aimed at translating clinical evidence to practical setting. The 5th Annual Precision Medicine Through Plasma: Using Liquid Biopsies in Contemporary Oncology Care, a half-day program sponsored by Physicians’ Education Resource®, LLC (PER®) is one such event. The live, interactive webcast, chaired by Benjamin P. Levy, MD, will take place on November 20. The agenda will provide clinical context on the current trends for the use of liquid biopsy for the treatment of patients with cancer and how it continues to evolve and proves its utility alongside direct tumoral biopsy.

To learn more about the webcast and to register, visit gotoper.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

REFERENCES
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ONE YEAR AGO, FEW, if any, objective observers would have suggested that our country would be faced with a situation where 30% to 40% of the adult population in the United States were seriously hesitant, apathetic about, or essentially refusing to receive one of the 3 COVID-19 vaccines approved by the FDA. Of the more than 3000 counties that comprise the US, the percentage of individuals who are currently fully vaccinated is less than 30%, despite the well-documented real-world success data for the vaccines in preventing serious illness, hospitalizations, and death from COVID-19 infection. Evidence supports the benefits of the approved vaccines against the far more infectious delta COVID-19 variant, and those currently unvaccinated are facing an increasing risk if infected in the absence of a complete vaccine program. Additionally, recent data for individuals requiring hospitalization because of COVID-19 have confirmed the potentially devastating effect of the event, with approximately half of patients experiencing serious complications, including those younger than 60 years.

The scientific evidence of benefit and overall safety data of the vaccines are overwhelming, but these data have been and continue to be insufficient to overcome a variety of objections, misconceptions, and profound misinformation regarding the products. Consider, for example, the observation that despite a rapid increase in the number of cases in the region, only one-third of individuals in Baxter County, Arkansas, are immunized and only half of the staff of Baxter Regional Medical Center have received the vaccine. This example emphasizes the remarkably disturbing situation in the US, where objective scientific data related to the COVID-19 pandemic are increasingly politicized. Although some have attempted to vastly oversimplify the situation, vaccine hesitancy may have far more to do with underlying philosophical perspectives than with the science itself. Specifically, observers have acknowledged a focus on personal choice—the right to be left alone—vs responsibility to others in a group. This perspective is consistent with a rejection of both mask and vaccine mandates. There is also a deep-seated objection by certain individuals to government or academic elites who may appear condescending to ordinary citizens in their rhetoric, pronouncements, and proposed/mandated regulations. Conversely, those in favor of vaccination may have a stronger philosophical focus on a personal responsibility to assist others within society.

However, despite the admitted limitations of these broad generalizations, evidence supports the general conclusion that, although these perspectives are not absolute nor do they adequately characterize all or even most individuals within the 2 dominant political
parties in the US, past voting patterns have followed personal decisions regarding vaccination against COVID-19.

Again, in the opinion of this commentator, the apparent differences in the reluctance of many to be vaccinated noted above make a critical statement about highly personal beliefs regarding the role of government and its agencies as well as the pronouncements of experts in decisions to be made about the health and welfare of the individuals and their own families rather than a statement regarding acceptance of the role and value of science in their lives.

Finally, frequently changing recommendations by government officials and public health leadership (ie, masks vs no masks indoors or for children in schools; how many people can attend an indoor or outdoor sporting event; who makes these decisions, etc), as well as the understandable but most difficult suggestion that vaccinated individuals should be treated differently from the unvaccinated individuals, has served only to intensify feelings and beliefs that further polarize the population.

Now the question must be asked: What is the relevance of the above discussion to cancer management and major public health initiatives designed to reduce the burden of malignant disease? A recent example from Tennessee demonstrates the severity of the current situation as it relates to vital cancer prevention efforts. It was recently reported that the health officials there ordered the discontinuation of specific outreach to adolescents for all approved routine vaccines, including HPV vaccination, following pressure from certain members of the legislature regarding efforts by the health agency to encourage COVID-19 vaccination.7

This statement needs to be repeated: Health officials in the state of Tennessee have, at least temporarily, halted essential efforts that have been documented to prevent the ultimate development of cervical cancer and other HPV-associated malignancies, which includes more than half of all head and neck cancers in the US. Does it need to get scarier than this for the entire cancer establishment to demand the reversal of this decision and to hopefully prevent such ill-informed and dangerous decisions in the future?

REFERENCES
Pembrolizumab Plus Chemotherapy Moves Ahead in TNBC

The FDA has approved the combination of pembrolizumab (Keytruda) plus chemotherapy for the treatment of patients with high-risk, early-stage triple-negative breast cancer (TNBC). Specifically, the combination is indicated for a total of 8 cycles prior to surgery followed by pembrolizumab monotherapy for 9 cycles following surgery.

The decision was supported by data from the phase 3 KEYNOTE-522 trial (NCT03036488), which showed that the regimen prolonged event-free survival vs neoadjuvant chemotherapy alone.

With a median duration of response of 39.0 months, the addition of pembrolizumab significantly reduced the risk of disease progression or death by 37% compared with chemotherapy alone (HR, 0.63; 95% CI, 0.48-0.82, P=.00031). Additionally, the combination reduced the risk of death by 28% vs chemotherapy alone (HR, 0.72; 95% CI, 0.51-1.02; P=.03214). However, these data have not crossed the boundary for statistical significance.

These data also supported the FDA’s decision to convert the November 2020 accelerated approval of pembrolizumab plus chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 with a combined positive score of 10 or more to a regular approval.

Approval Solidifies Role of Pembrolizumab/Lenvatinib for Advanced Endometrial Carcinoma

The FDA has granted a regular approval to the combination of pembrolizumab (Keytruda) plus lenvatinib (Lenvima) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression after previous systemic therapy in any setting, and who are not candidates for curative surgery or radiation.

The conversion from an accelerated approval to a regular approval was based on findings from the phase 3 KEYNOTE-775 (NCT03517449) study, in which the combination significantly improved overall survival (OS) and progression-free survival (PFS) compared with investigator’s choice of chemotherapy in the form of doxorubicin or paclitaxel.

The median OS for the doublet was 17.4 months (95% CI, 14.2-19.9) vs 12.0 months (95% CI, 10.8-13.3) for chemotherapy; this yielded a 32% reduction in the risk of death (HR, 0.68; 95% CI, 0.56-0.84; P=.0001) vs chemotherapy. Additionally, the median PFS for the combination and for chemotherapy was 12.0 months (95% CI, 10.8-13.3) for chemotherapy; this yielded a 32% reduction in the risk of death (HR, 0.68; 95% CI, 0.56-0.84; P=.0001).

Belumosudil Gets Green Light in GVHD

The FDA has approved belumosudil (Rezurock) for the treatment of adult and pediatric patients 12 years and older with chronic graft-vs-host disease (GVHD) following failure of at least 2 prior lines of systemic therapy. The approval of the kinase inhibitor was supported by data from the phase 2 KD025-213 trial (NCT03640481), in which 65 patients were treated with 200 mg belumosudil daily. Data from the trial showed that the agent elicited an overall response rate of 75% (95% CI, 63%-85%) through cycle 7, day 1 of treatment; the complete response rate was 6% and the partial response rate was 69%.

Notable efficacy data points included a 1.8-month median time to first response with the agent, with 62% of patients who responded not needing new systemic therapy for at least 1 year. The median duration of response was 1.9 months.

FDA Releases Complete Response Letter for Retifanlimab for SCAC

The FDA has issued a complete response letter to Incyte Corporation, stating that more data are needed to demonstrate the clinical benefit of retifanlimab (INCMGA 0012). The manufacturer was seeking approval of the PD-L1 inhibitor for the treatment of adult patients with locally advanced or metastatic squamous cell carcinoma of the anal canal (SCAC) who have progressed on, or who are intolerant of, platinum-based chemotherapy.

In June 2021, the agency’s Oncologic Drugs Advisory Committee voted 13 to 4 to delay a decision regarding an accelerated approval. The biologics license application was supported by data from the phase 2 POD1UM-202 trial (NCT03597295), which evaluated 94 patients with platinum-refractory SCAC including those positive for HIV.

The inhibitor elicited an objective response rate of 13.8% (95% CI, 7.6%-22.5%), which included a complete response rate of 1.1%, a partial response rate of 1.1%, and a stable disease rate of 35.1%. The immunotherapy is being investigated in combination with carboplatin and paclitaxel vs placebo in patients with inoperable locally recurrent of metastatic SCAC who have not received prior systemic chemotherapy in the ongoing phase 3 POD1UM-303/InterAACT 2 trial (NCT04472429).

Bristol Myers Squibb Withdraws Nivolumab HCC Indication Following FDA Review

In consultation with the FDA, Bristol Myers Squibb has voluntarily withdrawn the indication for nivolumab (Opdivo) as a monotherapy for patients with hepatocellular carcinoma (HCC) who were previously treated with sorafenib (Nexavar) from the US market.

The decision to retract the indication for the PD-1 inhibitor was based on the agency’s evaluation of accelerated approvals for checkpoint inhibitors that have not met their postmarketing requirements. Nivolumab failed to demonstrate confirmatory benefit in the phase 3 CheckMate 459 trial (NCT02576509) that compared nivolumab with sorafenib in the frontline setting in 1099 patients with unresectable HCC. Statistical significance was not met for its primary end point of overall survival (HR, 0.85; 95% CI, 0.72-1.02; P=.0752).

In September 2017, the FDA granted accelerated approval to nivolumab for the treatment of patients with HCC after prior sorafenib—regardless of PD-L1 status—based on data from the phase 1/2 CheckMate040 trial (NCT01658878). Findings from the 154 evaluable patients showed that the agent elicited an overall response rate of 18.2%, including a 3.2% complete response rate.
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Investigational

Ph 2 Clinical Trials
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- PD-L1 positive or negative status
- Tumors with EGFR, ALK, ROS mutations acceptable
- ECOG PS 0 – 1 (Fully active or able to carry out light work or activity)
- At least one tumor that can be safely removed by surgery for TIL and a second measurable tumor for response assessment

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Solid tumor trial NSCLC cohorts: NCT03645928

TIL Therapy is an investigational therapy and has not been approved for any indication by the United States Food and Drug Administration (USFDA) or any other regulatory agency. The safety and effectiveness of this study has not been determined.
Drug Spotlight | SACITUZUMAB GOVITECAN-HZIY (TRODELVY)

Tagawa Takes Stock of Future of Sacituzumab Govitecan in Urothelial Carcinoma

by JACKIE COLLINS

SACITUZUMAB GOVITECAN-HZIY (TRODELVY), a Trop-2-directed antibody-drug conjugate (ADC) with an SN-38 payload, has carved out a role in the treatment landscape for patients with locally advanced or metastatic urothelial cancer following accelerated approval by the FDA.

Specifically, the indication applies to patients whose disease has progressed following treatment with platinum-containing chemotherapy and either a PD-1 or a PD-L1 inhibitor. The decision was based on efficacy and safety data from the phase 2 TROPHY U-01 trial (NCT03547973), a multicohort, open-label clinical study. The agent elicited a confirmed objective response rate of 27.7% (95% CI, 19.6%-36.9%) comprising a 5.4% complete response rate and 22.3% partial response rate among 112 treated patients. The median duration of response was 7.2 months.

In an interview with OncologyLive®, Scott T. Tagawa, MD, MS, professor of medicine and urology at Weill Cornell Medicine and attending physician at NewYork-Presbyterian/Weill Cornell Medical Center, discussed the evolving treatment landscape and attending physician at NewYork-Presbyterian/Weill Cornell Medical Center, discussed the evolving treatment landscape of urothelial cancer that comes with the introduction of sacituzumab govitecan.

Q Please provide your thoughts on the treatment landscape and where sacituzumab govitecan fits in.

In terms of what was available before the approval, [treatment options were limited to] platinum-based chemotherapy, immune checkpoint inhibition, either PD-1 or PD-L1 inhibition, FGFR inhibition with a kinase inhibitor, and then, most recently, enfortumab vedotin-ejfv [Padcev], which was the first ADC [to receive] accelerated approval for urothelial carcinoma, and then full approval and a broadened [label].

The difference with sacituzumab govitecan has to do with the target, meaning Trop-2, which is a different target than other available drugs. The target is more important in terms of differentiation in the toxin, and for sacituzumab govitecan SN–38, which is the toxin, is a bit weaker than some of the toxins used in ADCs. The construct is designed to release the toxin inside the tumor but also near the tumors [in the microenvironment], so the linkers are not quite as tight.

In data from the primary trial that led to the approval, 10 patients received enfortumab vedotin prior to enrollment in the trial, and in a subset analysis the response rate was the same whether they were exposed to the agent or not. Although there were not a tremendous number of patients who have received both [enfortumab vedotin and sacituzumab govitecan], now there are dozens of patients who have.

The response rate demonstrated that this drug was effective for patients with pretreated, advanced urothelial carcinoma. The available data are from the nonrandomized TROPHY-U-01 trial, which had 5 cohorts, and cohort 1 was the main confirmatory population, [which included patients who were] post platinum-based chemotherapy, post-immune checkpoint inhibitor.

Q What adverse events (AEs) do clinicians need to be aware of when prescribing sacituzumab govitecan?

Myelosuppression, specifically neutropenia, is one of the major AEs to watch out for and it is relatively easily managed with dose reductions or delays if warranted. Neutropenia is something that occurred in a large percentage of this patient population; incidence was a little less than 50% in this data set, but high-grade neutropenia was reported for more than a third of patients, which translated into a 10% febrile neutropenia rate.

The other major AE is diarrhea. Approximately 10% of patients experienced grade 3 or 4 events, and grade 1 or 2 events were reported in more than half the patients. It’s important to note to the prescribers, as well as to the patients, that in my experience, diarrhea didn’t tend to persist throughout the course of therapy, but was more intermittent and related to dosage. Because it’s reasonably common, I make sure that my patients have an over-the-counter antidiarrheal at home. A small percentage of patients may need to go on prescription-strength drugs and/or have reduction in dose. But largely, because of the limited number of days and reasonably effective management with over-the-counter medicines, it’s an OK trade-off for what the response rate is in this refractory patient population.

Q What does the future hold for sacituzumab govitecan?

The landscape is shifting, and we hope to move these agents upstream. We’re looking not just for improvements in survival and quality of life, but increased cures in the either non–muscle invasive setting or muscle-invasive setting in combination with local therapy.

There are things that are clear and ongoing right now: The pivotal TROPICS-04 trial [NCT04527991]—the data of which are hopefully positive and will lead to full approval of sacituzumab govitecan for pretreated, urothelial carcinoma, and then, more importantly, the first approval of the drug outside of the United States.

I briefly mentioned that the TROPHY-U-01 trial has a number of other cohorts. Another cohort that many of us are excited about seeing what happens is cohort 3. There are things that are clear and ongoing right now: The pivotal TROPICS-04 trial [NCT04527991]—the data of which are hopefully positive and will lead to full approval of sacituzumab govitecan for pretreated, urothelial carcinoma, and then, more importantly, the first approval of the drug outside of the United States.

I briefly mentioned that the TROPHY-U-01 trial has a number of other cohorts. Another cohort that many of us are excited about seeing what happens is cohort 3. Here, investigators looked to see what happens if you combine sacituzumab govitecan with pembrolizumab [Keytruda]. We already know that that combination is safe now we’re waiting to see what happens in terms of efficacy. The cohorts not randomized against each other, but present different single-arm trial data.

REFERENCES

PIVOTAL CLINICAL TRIAL

TROPHY-U-01 (NCT03547973) was a multicenter, single-arm trial evaluating sacituzumab govitecan in patients with locally advanced or metastatic urothelial cancer (mUC) who have received platinum-containing chemotherapy and either a PD-1 or a PD-L1 inhibitor.

**BASELINE PATIENT CHARACTERISTICS:**

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Median number of prior lines of therapy (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (33-90)</td>
<td>3 (1-8)</td>
</tr>
</tbody>
</table>

**Types of prior lines of therapy (n = 112)**

- Cisplatin: 65%
- Carboplatin: 21%
- Both cisplatin and carboplatin: 13%
- Enfortumab vedotin: 9%

**Metastases at baseline**

- Visceral: 67%
- Liver: 34%

**ECOG performance status**

- 0: 28%
- 1: 72%

**FDA approval—April 13, 2021**

The FDA grants accelerated approval to sacituzumab govitecan-hziy (Trodelvy) for the treatment of patients with locally advanced or metastatic urothelial cancer (mUC) who have received platinum-containing chemotherapy and either a PD-1 or a PD-L1 inhibitor.

**Mechanism of action:**

- Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate, which selectively binds to Trop-2–expressing cancer cells. It consists of an antibody highly specific for Trop-2 with a hydrolysable linker that releases SN-38 cytotoxic payload extracellularly, initiating a bystander effect. The agent has a high drug to antibody ratio (7:6:1).

**Dose:**

- Premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended.
- Administer as an intravenous infusion
  - 10 kg/m² once weekly on days 1 and 8 of 21-day treatment cycles
  - First infusion: administer over 3 hours
  - Subsequent infusions: administer over 1 to 2 hours

**How supplied:**

- 180-mg lyophilized powder in single-dose vials for reconstitution

**Company:** Immunomedics Inc

**Efficacy in the Trophy-U-01 Trial**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sacituzumab govitecan (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>27.7% (19.6%-36.9%)</td>
</tr>
<tr>
<td>CR</td>
<td>5.4%</td>
</tr>
<tr>
<td>PR</td>
<td>22.3%</td>
</tr>
<tr>
<td>Number of responders</td>
<td>31</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>7.2 (4.7-8.6)</td>
</tr>
<tr>
<td>Range, months</td>
<td>1.4-13.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Sacituzumab govitecan (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>72%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68%</td>
</tr>
<tr>
<td>Nausea</td>
<td>66%</td>
</tr>
<tr>
<td>Any infection</td>
<td>50%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>49%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>41%</td>
</tr>
<tr>
<td>Constipation</td>
<td>34%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34%</td>
</tr>
</tbody>
</table>

**Commonly reported adverse effects in Trophy-U-01 trial**

**Warnings and precautions**

- Hypersensitivity and infusion-related reactions
- Nausea and vomiting
- Increased risk in adverse events in patients with reduced UGT1A1 activity
- Embryo-fetal toxicity

**Box Warning**

- **Neutropenia:** Monitor blood counts during treatment. If absolute neutrophil count is below 1500 mm³ or neutropenic fever occurs, withhold sacituzumab govitecan. Administer granulocyte colony stimulating factor for secondary prophylaxis. Should febrile neutropenia occur initiate anti-infective treatment without delay.
- **Diarrhea:** Administer atropine if not contraindicated for early diarrhea of any severity. For late diarrhea, evaluate infectious causes and if negative initiate loperamide. Withhold treatment until resolved to grade 1 and reduce subsequent doses.

**Reference**

INDICATION
XPOVIO® (selinexor) is a prescription medicine approved:
• in combination with bortezomib and dexamethasone (XVd) to treat adult patients with multiple myeloma who have received at least one prior therapy.

IMPORTANT SAFETY INFORMATION
Thrombocytopenia: XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia was reported in patients with multiple myeloma. Thrombocytopenia is the leading cause of dosage modifications. Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first 3 months of treatment. Monitor patients for signs and symptoms of bleeding. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia: XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection. Monitor more frequently during the first 3 months of treatment. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity: XPOVIO can cause severe gastrointestinal toxicities in patients.

Nausea/Vomiting/Diarrhea: Provide prophylactic antiemetics or treatment as needed.

Anorexia/Weight Loss: Monitor weight, nutritional status, and volume status at baseline and throughout treatment and provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

Hyponatremia: XPOVIO can cause severe or life-threatening hyponatremia. Monitor sodium level at baseline and throughout treatment.

Serious Infection: XPOVIO can cause serious and fatal infections. Atypical infections reported after taking XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Neurological Toxicity: XPOVIO can cause life-threatening neurological toxicities. Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity. Advise patients to refrain from driving and engaging in hazardous occupations or activities until the neurological toxicity fully resolves. Institute fall precautions as appropriate.
Embryo-Fetal Toxicity: XPOVIO 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 and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Cataracts: New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataract requiring clinical intervention was reported.

ADVERSE REACTIONS
The most common adverse reactions (ARs) (≥20%) in patients with multiple myeloma who received XVd were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract, and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

Fatal ARs occurred in 6% of patients within 30 days of last treatment. Serious ARs occurred in 52% of patients. Treatment discontinuation rate due to ARs was 19%. The most frequent ARs requiring permanent discontinuation in >2% of patients included fatigue, nausea, thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting. Adverse reactions led to XPOVIO dose interruption in 83% of patients and dose reduction in 64% of patients.

USE IN SPECIFIC POPULATIONS
No overall difference in effectiveness of XPOVIO was observed in patients >65 years old when compared with younger patients. Patients ≥65 years old had a higher incidence of discontinuation due to an adverse reaction (AR) and a higher incidence of serious ARs than younger patients. The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on XPOVIO pharmacokinetics is unknown.

Please see full Prescribing Information.
To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Reference: 1. XPOVIO (selinexor) [prescribing information]. Newton, MA: Karyopharm Therapeutics Inc.; April 2021.
**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

This Brief Summary is not intended to provide all the information needed to use XPOVIO safely and effectively. Please see XPOVIO Full Prescribing Information at XPOVIOpro.com.

**INDICATIONS AND USAGE**

XPOVIO is a nuclear export inhibitor indicated:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

**WARNINGS AND PRECAUTIONS**

**Thrombocytopenia**

XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia is the leading cause of dosage modifications. Thrombocytopenia was reported in 92% of patients and severe (Grade 3-4) thrombocytopenia was reported in 43%. The median time to first onset was 22 days for any grade thrombocytopenia and 43 days for Grade 3 or 4 thrombocytopenia. Bleeding occurred in 16% of patients with thrombocytopenia, clinically significant bleeding (Grade ≥3 bleeding) occurred in 4% of patients with thrombocytopenia, and fatal hemorrhage occurred in 2% of patients with thrombocytopenia. Permanent discontinuations of XPOVIO due to thrombocytopenia occurred in 2% of patients.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction.

**Neutropenia**

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection. Neutropenia was reported in 48% of patients and severe neutropenia (Grade 3-4) was reported in 12% of patients. The median time to onset of the first event was 23 days for any grade neutropenia and 40 days for Grade 3-4 neutropenia. Febrile neutropenia was reported in <1% of patients. Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction.

**Gastrointestinal Toxicity**

XPOVIO can cause severe gastrointestinal toxicities. Nausea/Vomiting

With use of antiemetic prophylaxis (88% of patients), nausea was reported in 50% of patients and Grade 3 nausea was reported in 8% of patients. The median time to onset of the first event was 6 days. Vomiting was reported in 21% of patients and Grade 3 vomiting was reported in 4%. The median time to onset of the first event was 8 days. Permanent discontinuation due to nausea occurred in 31% of patients and due to vomiting occurred in 21% of patients.

Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea

Diarrhea was reported in 32% of patients and Grade 3 diarrhea was reported in 6% of patients. The median time to onset of the first event was 50 days. Permanent discontinuation due to diarrhea occurred in 1% of patients.

Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

**Anorexia/Weight Loss**

Anorexia was reported in 35% of patients and Grade 3 anorexia was reported in 3.6% of patients. The median time to onset of the first event was 35 days. Permanent discontinuations due to anorexia occurred in 2.1% of patients. Weight loss was reported in 26% of patients and Grade 3 weight loss was reported in 2.1% of patients. The median time to onset of the first event was 58 days. Permanent discontinuation due to weight loss occurred in 1% of patients.

Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction. Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

**Hyponatremia**

XPOVIO can cause severe or life-threatening hyponatremia. Hyponatremia was reported in 58% of patients and Grade 3-4 hyponatremia was reported in 14% of patients. The median time to first onset was 21 days for any grade hyponatremia and the median time to first onset for Grade 3 or 4 hyponatremia was 22 days.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose or permanently discontinue based on severity of the adverse reaction.

**Serious Infection**

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia. 69% of patients experienced any grade of infection. Grade ≥3 infections were reported in 32% of patients, and deaths from infections occurred in 3% of patients. The most frequently reported Grade ≥3 infection was pneumonia in 14% of patients, followed by sepsis in 4.1% and upper respiratory tract infection in 3.6%.

Atypical infections reported after XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection. Monitor for signs and symptoms of infection, evaluate and treat promptly.

**Neurological Toxicity**

XPOVIO can cause life-threatening neurological toxicities. Neurological adverse reactions (excluding peripheral neuropathy) including dizziness, syncope, depressed level of consciousness, vertigo, amnesia and mental status changes (including delirium and confusional state) occurred in 26% of patients and severe events (Grade 3-4) occurred in 3.6% of patients. The median time to the first event was 29 days.

Permanent discontinuation due to neurological adverse reactions occurred in 2.1% of patients.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

**Embryo-Fetal Toxicity**

XPOVIO 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 and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

**Cataract**

New onset or exacerbation of cataract has occurred during treatment with XPOVIO. The incidence of new onset or worsening cataracts requiring clinical intervention was reported in 22% of patients. The median time to new onset of cataract was 228 days and was 237 days for worsening of cataract in patients presenting with cataract at start of XPOVIO therapy. Treatment of cataracts usually requires surgical removal of the cataract.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

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

**Multiple Myeloma**

**XPOVIO in Combination with Bortezomib and Dexamethasone (SVd)**

The safety of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON. Patients were randomized to receive XPOVIO 100 mg orally once weekly in combination with bortezomib and dexamethasone (SVd) (n=195) or bortezomib and dexamethasone (Vd) (n=204). Among patients who received XPOVIO, the median duration of XPOVIO treatment was 29 weeks (range: 1 to 120 weeks) and the median dose was 80 mg (range: 30 to 137 mg) per week.

Serious adverse reactions occurred in 52% of patients who received XPOVIO in combination with bortezomib and dexamethasone. Serious adverse reactions in >3% of patients included pneumonia (4%), sepsis, diarrhea and vomiting (4% each). Fatal adverse reactions occurred in 6% of patients within 30 days of last treatment, including pneumonia (n=3) and sepsis (n=3).

Grade ≥2 peripheral neuropathy, a pre-specified key secondary endpoint, was lower in the SVd arm (2%) compared to the Vd arm (3%); odds ratio 0.50 (95% CI 0.32, 0.79). The median treatment duration was 30 weeks (range: 1-120 weeks) in patients who received once weekly SVd as compared to 32 weeks (range: 1-122 weeks) in patients who received twice weekly Vd.

Permanent discontinuation of XPOVIO due to an adverse reaction occurred in 19% of patients.

Adverse reactions which resulted in permanent discontinuation of XPOVIO in >2% of patients include fatigue (3.5%), nausea (3.1%), thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting (2.1% each).
Table 5: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received XPOVIO in Combination with Bortezomib and Dexamethasone (SVd) with a Difference Between Arms of >5% Compared to Vd in BOSTON

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Weekly SVd (n=195)</th>
<th>Twice Weekly Vd (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>General Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Key: Sx1=v1-bortezomib-dexamethasone

XPOVIO Brief Summary

XPOVIO is a nuclear export inhibitor indicated:

- for the treatment of patients with multiple myeloma who have received prior therapy and whose disease is no longer responding to standard therapies.
- for the treatment of patients with relapsed or refractory multiple myeloma, including those who have received prior therapy with a proteasome inhibitor and an immunomodulatory drug, as well as those who have received prior therapy with carfilzomib.

Clinical Trials Experience

In the Phase 3 clinical trial, patients were randomized to receive either XPOVIO plus lenalidomide and dexamethasone (n=194) or lenalidomide and dexamethasone alone (n=203). The primary endpoint was the median time to progression (TTP). The median TTP was 15.1 months in the XPOVIO arm compared to 10.5 months in the control arm (HR 0.68, p=0.0006). Additionally, the response rate was 99% in the XPOVIO arm compared to 85% in the control arm (p=0.02).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose (see Dose). Advise pregnant women of the risks to a fetus.

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

Data

Animal studies

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

XPOVIO can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Males

Advise males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Infertility

Females and Males

Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the 195 patients with multiple myeloma who received XPOVIO in combination with bortezomib and dexamethasone, 56% were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger patients. When comparing patients 65 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 13%) and a higher incidence of serious adverse reactions (56% vs 47%).

PATIENT COUNSELING INFORMATION

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

Dosing Instructions:

- Instruct patients to take XPOVIO exactly as prescribed.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications exactly as directed.
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first three months of treatment.
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment.

Hematologic Adverse Reactions

Thrombocytopenia

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment. Advise patients to report signs of bleeding right away.

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia.

Neutropenia

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection. Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Gastrointestinal Adverse Reactions

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist.

Advise patients that they may experience weight loss or decreased appetite. Advise patients to report decreased appetite and weight loss.

Hyponatremia

Advise patients that they may develop low sodium levels (hyponatremia). Most cases of hyponatremia were not associated with infection-related signs or symptoms (e.g., chills, fever).

Neurotoxicity

Advise patients that they may experience confusion and dizziness. Advise patients to report symptoms of neurological toxicity right away. Advise patients not to drive or operate hazardous machinery until the neurological toxicity fully resolves. Advise patients to use fall prevention measures as warranted.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to contact their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the final dose.

Cataract

Advise patients of the potential risk of worsening or new onset of cataract, that may require surgery. Advise patients to readily inform their healthcare professionals of changes in vision (i.e. blurred vision) and that ophthalmologic evaluation may be performed as clinically indicated.

Fatigue

Advise patients that they may experience fatigue.

Lactation

Advise women not to breastfeed during treatment with XPOVIO and for 1 week after the final dose.

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and other anti-nausea agents prior to and during treatment with XPOVIO.

Advise patients to speak with their physician about other medications they are currently taking and before starting any new medication.
Although the Precision Medicine era is in full swing in oncology, 3 emerging biomarkers for tailoring therapy need further clinical and technical clarity to support robust use in daily practice, according to experts. Academic, government, and industry investigators are collaborating on projects intended to expand the understanding and ultimately the clinical utility of these markers: circulating tumor DNA (ctDNA), tumor mutational burden (TMB), and homologous recombination deficiency (HRD).

Friends of Cancer Research, an advocacy group that helped pioneer the breakthrough therapy program and other regulatory advances, has brought together teams of experts to explore each of the biomarkers. The goal of the ctDNA project is to demonstrate whether changes in levels of this biomarker can be used to signal the efficacy of therapeutic strategies in a range of solid tumor types, whereas the objective of the TMB and HRD programs is to answer questions about differences in assays that assess these genomic signatures.

The quest to better understand these biomarkers comes amid an increase in FDA approvals of oncology therapies for specific subsets of patients with cancer based on the presence of a measurable biological feature, including recent novel agents associated with the markers under study, according to Mark Stewart, PhD, vice president of science policy at the Friends group (TABLE 1). He also noted that there has been an “exponential” increase in the number of clinical trials that integrate ctDNA, TMB, or HRD testing into the study design.

For Friends, the research partnerships are intended to “leverage new technologies and help expedite drug development,” Stewart said in an interview with OncologyLive®.

“What we’re seeing is that there’s not necessarily 1 way to define these biomarkers and assess them,” he said. “It does create a scenario where results from one test may not be interchangeable with another test.”

**Expanding the Utility of ctDNA Testing**

cDNA, defined as fragments derived from tumor cells undergoing apoptosis or necrosis, comprises a small fraction of circulating cell-free DNA (cfDNA) in the bloodstream of patients with cancer, with levels dependent on tumor burden, histologic type, and malignancy stage.

![Mark Steuart, PhD](image)
Investigators have sought to leverage cfDNA for liquid biopsies in solid tumors, and its potential as a tumor biomarker was first identified in 1994. In 2016, the FDA approved the first liquid biopsy test, cobas EGFR Mutation Test v2, which is indicated for the detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in the plasma of patients with non–small cell lung cancer (NSCLC). The assay is now designated as a companion diagnostic for patients with NSCLC who are candidates for therapy with erlotinib (Tarceva), osimertinib (Tagrisso), and gefitinib (Iressa).

Although several tumor-profiling assays that use next-generation sequencing (NGS) technology on plasma samples have since gained approvals, the use of ctDNA has been limited in clinical practice. The Friends’ ctDNA for Monitoring Treatment Response (ctMoniTR) Project is seeking to establish whether changes in ctDNA correlate with responses to therapy for a broad range of tumor types, thus expanding its potential.

In August 2020, the Friends group reported findings from its comparison of outcomes for pooled data involving 200 patients with advanced NSCLC treated with PD-1/PD-L1 immune checkpoint inhibitors whose ctDNA levels had been measured with 5 assays. The results showed that changes in ctDNA measurements of variant allele frequency (VAF) levels from baseline were associated with overall survival (OS), progression-free survival (PFS), and treatment response.

The data demonstrated that VAF levels (strong increase, intermediate, and strong decrease) correlated with outcomes. Patients with a 50% or higher decrease in maximum VAF from baseline during therapy had a stronger association with better OS (P < .0001) and PFS (P = .0002) than did those with an increase or weak decrease. A strong decrease in maximum VAF also correlated with improved rates of partial responses or better.

In June 2021, Friends launched the next step of the ctMoniTR Project: collecting data from more than 25 studies involving over 3000 patients with diverse malignancies, including lung, melanoma, thyroid, breast, and head and neck cancers, who received treatment with a variety of therapies. Investigators will analyze the data to determine whether ctDNA can be used to identify whether patients are responding to treatment earlier than other methods of evaluation. Preliminary results are expected to be released in 2022.

The findings may help answer the question of whether responses to therapy can be monitored serially with a blood test, according to Matthew D. Hellmann, MD, a medical oncologist at Memorial Sloan Kettering.

### TABLE. Select FDA-Approved Companion Diagnostics

<table>
<thead>
<tr>
<th>Assay</th>
<th>Description</th>
<th>Tumor type, agent, and alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood-based tests for solid tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guardant360 CDx</td>
<td>Detects genetic alterations in ctDNA from plasma of peripheral whole blood</td>
<td>NSCLC Osimertinib (Tagrisso)—EGFR exon 19 deletions, exon 21 (L858R) mutations, and T790M alterations</td>
</tr>
<tr>
<td>FoundationOne Liquid CDx</td>
<td>NGS test that detects aberrations in more than 300 genes using ctDNA isolated from plasma derived from peripheral whole blood</td>
<td>NSCLC Gefitinib (Iressa), osimertinib, erlotinib (Tarceva)—EGFR exon 19 deletions and exon 21 (L858R) alterations</td>
</tr>
<tr>
<td>cobas EGFR Mutation Test v2</td>
<td>Detects mutations in ctDNA from plasma derived from whole blood</td>
<td>Prostate Olaparib (Lynparza)—BRCA1/2, ATM alterations, Rucaparib (Rubraca)—BRCA1/2 alterations</td>
</tr>
<tr>
<td>BRACAnalysis CDx</td>
<td>Detects BRCA1/2 mutations using genomic DNA from whole blood specimens</td>
<td>Ovarian Olaparib—BRCA1/2 alterations, Rucaparib—BRCA1/2 mutations, Talazoparib (Talzenna)—BRCA1/2 mutations</td>
</tr>
<tr>
<td>Homologous recombination deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FoundationOne CDx</td>
<td>NGS assay for detecting alterations in 324 genes in several genomic signatures in DNA isolated from tumor tissue</td>
<td>Prostate cancer Olaparib—alterations in 14 HRR genes</td>
</tr>
<tr>
<td>Myriad myChoice CDx</td>
<td>NGS assay that detects BRCA1/2 gene mutations and determines a genomic instability score using DNA isolated from tumor tissue</td>
<td>Ovarian cancer Olaparib, niraparib (Zejula)—BRCA1/2 mutations and/or positive genomic instability score</td>
</tr>
<tr>
<td>Tumor mutational burden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FoundationOne CDx</td>
<td>Same as above</td>
<td>Solid tumors Pembrolizumab (Keytruda)— ≥ 10 mut/Mb</td>
</tr>
</tbody>
</table>

cDNA, cell-free DNA; ctDNA, circulating tumor DNA; HRR, homologous recombination repair; mut/Mb, mutations per megabase; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer.
Cancer Center in New York, New York, who is participating in the ctMoniTR Project. Currently, ctDNA testing is used primarily for molecular profiling and genotyping of patients with known cancer, he noted. “This advance would expand the use of the ctDNA tests. The information from ctDNA dynamics would show not just whether there is a genetic alteration that can be targeted but what is happening in the patient in real-time, whether their cancer treatment is or isn’t working.”

Hellmann, a lung cancer specialist, has contributed to a growing body of evidence showing the clinical utility of ctDNA testing. In a pan-cancer analysis, Hellmann and colleagues studied ctDNA levels before and after therapy for patients treated with the PD-L1 inhibitor durvalumab (Imfinzi) in 3 clinical trials spanning 16 types of advanced cancers.15

Lower levels of pretreatment ctDNA were prognostically associated with improved OS among patients with the most prevalent cancer types in the study such as NSCLC (n = 333) and urothelial cancer (n = 226). And among a subset of patients with on-treatment ctDNA, a substantial decrease in ctDNA on-treatment significantly correlated with improved OS and PFS.15

In another report published in Cell in October 2020, colleagues from Stanford along with Hellmann described a model for a noninvasive assay incorporating pretreatment ctDNA with immune profiling for markers such as CD8 T cells and PD-L1 expression as well as early on-treatment ctDNA levels. The assay, DIREct-ON, accurately classified the likelihood of durable benefit for patients with NSCLC who received PD-L1 inhibitor therapy after 1 treatment cycle.16 Assays that measure ctDNA have the potential to help inform treatment across tumor types, Hellmann said. “I anticipate that this diagnostic tool will have broad relevance in clinical practice and research, including across the spectrum of cancer stages, from the earliest days to the latest stages, across the range of cancer types,” he said. “It could also expand across different types of treatments, from targeted treatment to chemotherapy to immunotherapy.”

For practicing oncologists to embrace such assays, clinical evidence would have to show that they are helpful in guiding clinical decision making, Hellmann said. “The first step is to prove that the information is useful—to show the clinical applicability of having the information on hand to be able to make treatment decisions,” he said. “Fundamentally, the primary goal of Friends of Cancer Research is to demonstrate that having an assessment of ctDNA during an early course of treatment would allow clinicians to have an early read on how patients are doing on the treatments they’re getting. That can be the foundation for wholly new paradigms for clinical treatment; you would know where there could be early transitions away from ineffective treatment or early addition of a new treatment. It could really change the way that we approach a given patient.”

MORE CLARITY FOR COMPLEX BIOMARKERS

When it comes to TMB and HRD, the Friends research teams are focused on helping to clarify the results of assays that have limited immediate clinical applications but are likely to be more frequently employed in cancer care in the future. “There’s a wide variation in how TMB and HRD are being

![FIGURE. Response Rates for Published Immunotherapy Studies Reporting TMB-based Outcomes](https://bit.ly/2TMkLoX)
defined, measured, and reported across these studies that are being published,” Stewart said. “This clearly highlights a lack of standardization and harmonization and how these markers are being used. As you could imagine, that can create scenarios where there might be confusion about how to appropriately use these tests, affecting their integration into clinical care.”

**TMB**

TMB, a measure of the number of somatic mutations per megabase (mut/Mb) of the tumor’s genome, currently is approved as a biomarker for 1 drug. In June 2020, the FDA granted an accelerated approval for the PD-1 inhibitor pembrolizumab (Keytruda) as treatment for adult and pediatric patients with unresectable or metastatic TMB-high (TMB-H) solid tumors (≥ 10 mut/Mb) that have progressed after prior therapy and who have no satisfactory alternative treatment options. The agency designated the FoundationOne CDx assay, which uses DNA isolated from formalin-fixed paraffin embedded tumor tissue specimens, as the companion diagnostic.

The approval was based on findings from the KEYNOTE-158 trial (NCT02628067) involving 102 patients with TMB-H tumors spanning 9 cancer types who received pembrolizumab monotherapy at 200 mg every 3 weeks. Tumor types included small cell lung, cervical, endometrial, and anal cancers.

After a median follow-up of 11.1 months, the objective response rate among patients with tumors with a TMB of 10 or more mut/Mb was 29% (95% CI, 21%-39%), including a 4% complete response rate. So far, the FoundationOne CDx assay is the only FDA-approved companion diagnostic for assessing TMB. The agency has also cleared the MSK-IMPACT assay for use as a tumor-profiling NGS test that can measure TMB. Meanwhile, a growing pipeline of commercial and laboratory-developed tests with different features may affect TMB estimations, according to a review by members of the TMB Harmonization Consortium that Friends organized. Differences in commercial and academic tests may include the numbers and types of genes, sequencing platforms, and bioinformatics protocols.

During the past 3 years, the consortium has identified sources of variability in testing methods and agreed on the creation of a universal reference standard that reconciles data from whole-exome sequencing, which was initially used in TMB research, with scores generated by targeted panels. The group then evaluated retrospective clinical trial data involving more than 1700 patients with diverse tumor types who were treated with immune checkpoint inhibitors. Overall, patients with TMB of 10 mut/Mb or higher had average response rates of 33% vs 13% for those with lower scores (FIGURE 21). Similar support for that definition of TMB-H was evident in a further analysis of response data for patients with scores in an “equivocal zone” between 10 and 15 mut/Mb.

As data mature, the Friends group anticipates a need for further consideration of how diagnostic test approvals can include patients with scores in the equivocal zone.

**HRD**

HRD is broadly defined as a defect in DNA repair mechanisms caused by loss of function in homologous recombination repair (HRR) genes, including those encoded by *BRCA1, BRCA2, RAD51, RAD51C, RAD51D,* and *PALB2.* In current clinical practice, the use of HRD testing has emerged as an important feature of selecting patients with ovarian cancer for PARP inhibitor therapy in certain settings.

Olaparib (Lynparza) is approved in combination with bevacizumab (Avastin) as maintenance therapy for patients with HRD-positive advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have responded to first-line platinum-based chemotherapy. Niraparib (Zejula) is indicated for patients with HRD-positive advanced ovarian, fallopian tube, or primary peritoneal cancer whose disease has progressed after 3 or more prior chemotherapy regimens. Both drugs carry additional indications that do not require HRD testing.

For both therapies, HRD status is defined as a deleterious *BRCA* mutation or genomic instability, as measured with the Myriad myChoice CDx assay, which generates an algorithmic measurement of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions using DNA isolated from tumor tissue.

As with TMB, the clinical applicability of HRD assessment is expected to grow as research continues. HRD can be defined in multiple ways, according to a working group that the European Society for Medical Oncology formed to investigate testing standards for the biomarker in ovarian cancer. Although current tests can predict the likelihood of a response to PARP inhibitor therapy for patients with ovarian cancer, more dynamic markers are needed to inform treatment decisions, the panel concluded.

Meanwhile, other malignancies are “enriched” for HRD, including prostate, pancreatic, and breast cancers. In May 2020, the FDA approved olaparib for patients with metastatic castration-resistant prostate cancer who have progressed following prior treatment and whose disease harbors mutations in HRR genes. The indication covers 14 HRR genes including *BRCA1/2.*

The decision was based on findings from the pivotal PROfound trial (NCT02987543), in which investigators used FoundationOne CDx on tumor tissue to test for HRG genes and Myriad’s BRACAnalysis CDx on blood samples to determine *BRCA* status. Both tests have been designated as companion diagnostics for the prostate cancer indication.

The Friends group also sees a lack of standardization in the definition, measurement, and reporting of HRD status. In December 2020, Friends launched its HRD Harmonization Project. Much like the group’s efforts on TMB, the project aims to improve the understanding of HRD assays and analyze the clinical context in which they are being used. Results are expected later this year and in 2022.

“I think efforts like this are really important—just to highlight that level of variability or to really understand and characterize how much variability does exist across different essays—and whether we can help reduce it so that as these [assays] are increasingly used in oncology care, physicians and patients can have confidence in the results,” Stewart said.
**SELECT SAFETY INFORMATION**

- **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.

- **CONSISTENT RESULTS WITH OR WITHOUT PRIOR ADJUVANT CHEMOTHERAPY**
  - Patients in the ADAURA trial are treated with **ORAL TAGRISSO FOR 3 YEARS** or until disease recurrence or unacceptable toxicity.

- **EXPLORATORY SUBGROUP RESULTS**
  - Exploratory subgroup results for patients with adjuvant chemotherapy was HR=0.16 (95% CI: 0.10, 0.26) and for patients without adjuvant chemotherapy was HR=0.23 (95% CI: 0.13, 0.40). The HR of 0.23 for TAGRISSO includes a 24-week benefit in DFS median (95% CI: 38.8, NE) and DFS rate at 2, 3, 4, and 5 years of 83%, 78%, 72%, and 66% compared with 50%, 44%, 38%, and 32% for placebo. 

- **REDUCTION IN RISK OF RECURRENCE OR DEATH**
  - HR=0.17 (95% CI: 0.12, 0.23); P<0.0001

- **TOLERABILITY**
  - Treatment with TAGRISSO is generally well tolerated. The most common (≥20%) adverse reactions, including laboratory abnormalities, were leukopenia, lymphopenia, hypertension, and decreased appetite.

- **EFFECTS ON LUNG FUNCTION**
  - 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 (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed.

- **CARDIOVASCULAR EVENTS**
  - The ADAURA study was conducted in stage II/IIIA NSCLC patients and evaluated the benefit of adjuvant TAGRISSO compared to placebo following surgery. The planned treatment duration was 3 years or until disease recurrence.

- **ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY**
  - **TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients**

- **PRIMARY ENDPOINT: DISEASE-FREE SURVIVAL IN PATIENTS WITH STAGE II/IIIA DISEASE (N=470)**
  - 1-year DFS rate 97%
  - 2-year DFS rate 90%
  - 3-year DFS rate 78%

- **BRIGHTER DAYS AHEAD FOR MORE EGFRm NSCLC PATIENTS**

- **TAGRISSO is a registered trademark of the AstraZeneca group of companies.©2021 AstraZeneca. All rights reserved. US-53002 4/21**
‡ Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.

• 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 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 if confirmed.

1 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 IIA), 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/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 3 years or until disease recurrence/unacceptable toxicity.2,4

Interim analysis of DFS for stage II/IIIA patients occurred after 1 year of treatment (median follow-up: 13 months). Median DFS 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/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 3 years or until disease recurrence/unacceptable toxicity.2,4

Heart rate-corrected QT (Qtc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1479 TAGRISSO-treated patients in clinical trials, 0.8% were found to have a Qtc >500 msec, and 3.1% of patients had an increase from baseline Qtc >60 msec. No Qtc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, 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.

INDICATIONS AND USAGE

TAGRISSO® (osimertinib) tablets, for oral use

INDICATIONS AND USAGE

TAGRISSO® (osimertinib) tablets, for oral use

INTERVENTION THERAPY

INTERVENTION THERAPY

Table 1. Recommended Dosage Modifications for TAGRISSO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (see Warnings and Precautions (5.4) in the full Prescribing Information)</td>
<td>Interstitial lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
<tr>
<td>Cardiac (see Warnings and Precautions (5.6) in the full Prescribing Information)</td>
<td>QTc interval prolongation</td>
<td>Discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

Dosage and Administration

Recommended Dosage Regimen

Cardiac (see Warnings and Precautions (5.6) in the full Prescribing Information)

Other (see Adverse Reactions (6.1) in the full Prescribing Information)

Adverse Reactions

Interstitial Lung Disease/Pneumonitis

Interstitial Lung Disease/Pneumonitis

Other (see Adverse Reactions (6.1) in the full Prescribing Information)

Adverse Reactions

Clinical Trials Experience

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

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials [ADAURA (n=337), FLAURA (n=279), and AURA3 (n=279)]. Two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], one dose-finding study [AURA1 (n=173)] (see Warnings and Precautions (5) in the full Prescribing Information). Among 1479 patients who received TAGRISSO, 81% were exposed for 6 months or longer and 66% were exposed for greater than one year. In this pooled safety analysis, the most common adverse reactions in >25% of patients were thrombocytopenia (38%), anemia (36%), neutropenia (34%), and hypertension (34%).

The data described below reflect exposure to TAGRISSO (80 mg daily) in 327 patients with EGFR mutation-positive metastatic NSCLC, and 558 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials [ADAURA (n=257), FLAURA (n=279), and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis who required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.
Clinically relevant adverse reactions in ADURA in <10% of patients receiving TAGRISSO were alopecia (8%), epistaxis (6%), interstitial lung disease (3%), palmar-plantar erythrodysesthesia syndrome (1.5%), keratitis (0.6%), QTc interval prolongation (0.6%), and erythema multiforme (0.3%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=337)</th>
<th>Placebo (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong>¹</td>
<td>All Grades</td>
<td>Grade 3 or higher</td>
</tr>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>44</td>
<td>3.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25</td>
<td>2.3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>24</td>
<td>1.3</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>20</td>
<td>1.8</td>
</tr>
</tbody>
</table>

¹ MTC TCA E4-V. ² Based on the number of patients with available follow-up laboratory data. Laboratory abnormalities in ADURA that occurred in ≥20% of patients receiving TAGRISSO were increased blood creatinine (10%), Prolonged QTC interval as assessed by ECG (4.3%), diarrhea (2.5%), and hyperglycemia (0.6%). QTc interval prolongation represents the incidence of patients who had a QTcF prolongation >500msec.

Table 4. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong>¹</td>
<td>All Grades</td>
<td>Grade 3 or higher</td>
</tr>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>59</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>0.7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>37</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>30</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>21</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>16</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>0.0</td>
</tr>
</tbody>
</table>

¹ MTC TCA E4-V. ² Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-treatment laboratory measurement available (TAGRISSO range: 367 - 273 and EGFR TKI comparator range: 256 - 388). Hyponatremia is based on the number of patients who had both baseline and at least one on-treatment laboratory measurement available (TAGRISSO (179) and EGFR comparator (191)).

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong>¹</td>
<td>All Grades</td>
<td>Grade 3 or higher</td>
</tr>
<tr>
<td></td>
<td>Any Grade (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>59</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>0.7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>37</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>30</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>26</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>21</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>16</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14</td>
<td>0.0</td>
</tr>
</tbody>
</table>

¹ MTC TCA E4-V. ² Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-treatment laboratory measurement available (TAGRISSO range: 367 - 273 and EGFR TKI comparator range: 256 - 388). Hyponatremia is based on the number of patients who had both baseline and at least one on-treatment laboratory measurement available (TAGRISSO (179) and EGFR comparator (191)).

Clinically relevant laboratory abnormalities in FLAURA that occurred in ≥20% of patients receiving TAGRISSO were increased blood creatinine (9%), QTc interval prolongation >500msec.
chemotherapy-treated patients. The trial population characteristics were: median age 67 years, age less than 65 (58%), female (64%), Asian (65%), never smokers (68%), and EGFR PS 0 or 1 (100%). Serious adverse reactions were reported in 16% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a total adverse reaction (ILD/pneumonitis).

Dose reductions occurred in 29% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neupropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO.

The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Table 6 and 7 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3.

Table 6. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3*

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3/4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>106 (38)</td>
<td>29 (22)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (40)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>6 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>39 (14)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Nail toxicity§</td>
<td>22 (8)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (5)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>15 (5.5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (4)</td>
<td>0.4 (0)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>17 (6)</td>
<td>0.7 (0)</td>
</tr>
<tr>
<td>*NCI CTCAE v4.0.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Includes stomatitis and mouth ulceration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡ Includes rash, general rash, erythema, rash macular, rash maccular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis, acneform dermatitis, pustules.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‖ Includes nail, skin, scarring, skin lacerations, eczema.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>§ Includes nail, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail dystrophy, nail infection, nail onychia, onychia, onychodys trophy, onychomadesis, paronychia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>¶ Includes pruritus, pruritus generalis, eyelid pruritus.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‌ Includes fatigue, asthenia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinically relevant adverse reactions in AURA3 in &lt;10% of patients receiving TAGRISSO were epistaxis (5%), interstitial lung disease (3%), alopecia (3%), palmar-planter erythrodysesthesia syndrome (1%), QT interval prolongation (1.4%), keratitis (1.1%), and erythema multiforme (0.7%). QT interval prolongation represents the incidence of patients who had a QTc interval &gt;500msec.</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3 (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or Grade 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43 (0)</td>
<td>79 (31)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 (8)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 (6)</td>
<td>47 (6)</td>
</tr>
</tbody>
</table>

The end of organogenesis (gestation days 2-20) was a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered between days 6 and 20, osimertinib caused an increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at 30 mg/kg/day during organogenesis through lactation, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [see Use in Specific Populations].

Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 6 weeks after the final dose.

Females and Males of Reproductive Potential

Based on animal data, TAGRISSO can cause malformations, embryonic lethality, and postnatal death at doses resulting in exposures 1.5 times or less than the human exposures at the clinical dose of 80 mg daily [see Use in Specific Populations].

Caution

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks following the final dose [see Use in Specific Populations].

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [see Use in Specific Populations].

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is unknown whether the effects on male fertility are reversible [see Nonclinical Toxicology].

Pediatric Use

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

Geriatric Use

Forty-three percent (43%) of the 1479 patients in ADAURA (n=237), FLAURA (n=279), AURA2 (n=279), AURA Extension (n=201), AURA3 (n=216), and AURA3 (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (25% vs 27%) and more frequent dose modifications for adverse reactions (32% vs 21%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) <15 - 90 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) [see Clinical Pharmacology].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action [see Clinical Pharmacology], TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose (see Data). Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

When administered to pregnant rats prior to embryonic implantation...
Lenvatinib Treatment Delivers Benefit for Patients With uHCC and Deteriorating Liver Function

by KRISTIE L. KAHL

FINDINGS FROM A POST HOC analysis of the phase 3 REFLECT trial (NCT01761266) have demonstrated that lenvatinib (Lenvima) remains the treatment of choice for patients with unresectable hepatocellular carcinoma (uHCC) associated with Child-Pugh class B (CP-B) liver function. Presenting data at the 2021 European Society for Medical Oncology Virtual World Congress on Gastrointestinal Cancer, investigators reported that patients experienced a tumor size reduction comparable with those of counterparts who have Child-Pugh class A (CP-A) disease.1

“The results of this post hoc analysis suggest that patients with uHCC whose liver function deteriorates to CP-B after initiation of therapy may continue to receive lenvatinib,” Jasmine Huynh, MD, and coauthors wrote in a poster presented during the meeting. Huynh is a second-year hematology/oncology fellow in the Department of Internal Medicine at UC Davis Health.

Results from the randomized, multicenter phase 3 REFLECT study, which led to the FDA’s approval of the agent for the first-line treatment of patients with uHCC,2 showed a benefit from lenvatinib, compared with sorafenib (Nexavar), irrespective of baseline liver function, including albumin-bilirubin (ALBI) grade 1 or 2 and CP score of 5 or 6.

However, of note, the trial enrolled patients with CP-A liver function per the study inclusion criteria, but not those with CP-B specifically.

“In the absence of any initial enrollment of patients with CP-B liver function, we conducted a post hoc exploratory analysis of key efficacy and safety outcomes in patients from REFLECT whose liver function had deteriorated to CP-B vs those whose liver function remained CP-A,” Huynh et al wrote of the rationale for the study.

The post hoc analysis assessed overall response rate (ORR) and landmark analyses that began after week 8; the latter included progression-free survival (PFS) and overall survival (OS), both in patients whose liver function had deteriorated to CP-B and in patients whose liver function remained CP-A.1 In the lenvatinib group, the CP-B and CP-A subgroups demonstrated ORRs of 28.3% (95% CI, 16.9%-39.7%) and 42.9% (95% CI, 38.1%-47.6%), respectively. In particular, for the CP-B subgroup of the lenvatinib arm, there were 0 complete responses (CRs), 17 (28.3%) partial responses (PRs), 17 (28.3%) patients with stable disease (SD), and 12 (20.0%) with progressive disease (PD); 14 (23.3%) were not evaluable (NE). In the CP-A subgroup, there were 10 (2.4%) CRs, 167 (40.4%) PRs, 142 (34.4%) with SD, and 67 (16.2%) with SD; 27 (6.5%) were NE.

In the sorafenib group, the CP-B and CP-A subgroups demonstrated ORRs of 8.5% (95% CI, 0.5%-16.5%) and 12.9% (95% CI, 9.7%-16.1%), respectively. For the CP-B subgroup of the sorafenib arm, there were 0 CRs, 4 (8.5%) PRs, 12 patients (25.5%) with
TREATMENT OPTIONS IN PATIENTS WITH CP-B LIVER FUNCTION. SUCH PATIENTS ARE RARELY INCLUDED IN CLINICAL TRIALS, THE INVESTIGATORS WROTE.

IN THE TRIAL, PATIENTS WITH uHCC WERE TREATED WITH LENVATINIB OR SORAFENIB. PATIENTS RECEIVED THE AGENT AT THE 400-MG Dose FOR THOSE WEIGHING MORE THAN 60 KG. PATIENTS ASSIGNED TO LENVATINIB, Dosage WAS BASED ON BODY WEIGHT: 12 MG/DAY FOR THOSE WEIGHING 60 KG OR MORE, AND 8 MG/DAY FOR THOSE WEIGHING LESS THAN 60 KG. PATIENTS ASSIGNED TO SORAFENIB RECEIVED THE AGENT AT THE 400-MG Dose TWICE DAILY.

AT BASELINE, PATIENTS WHOSE LIVER FUNCTION DETERIORATED TO CP-B WITHIN 8 WEEKS IN THE LENVATINIB AND SORAFENIB ARMS, 73.3% AND 75.4%, RESPECTIVELY, HAD AN ALBI SCORE OF 2, AND 60.0% AND 44.7% HAD A CP SCORE OF 6. SIMILARLY, AMONG THOSE WHOSE LIVER FUNCTION REMAINED CP-A WITHIN 8 WEEKS IN BOTH ARMS, 73.1% AND 75.4%, RESPECTIVELY, HAD AN ALBI SCORE OF 1, AND 83.5% AND 78.5% HAD A CP SCORE OF 5.

IN THE PRIOR ANALYSIS, TREATMENT WITH LENVATINIB DEMONSTRATED A HIGHER ORR, COMPARED WITH SORAFENIB, IN PATIENTS WITH A CP SCORE OF 5 (odds Ratio [OR], 4.88; 95% CI, 3.37-7.08) AND IN THOSE WITH A CP SCORE OF 6 (OR, 5.25; 95% CI, 2.32-11.85), AS WELL AS IN PATIENTS CLASSIFIED AS EITHER ALBI GRADE 1 (OR, 5.48; 95% CI, 3.70-8.10) OR ALBI GRADE 2 (OR, 5.37; 95% CI, 2.61-11.06).

For a full list of references, see the article at bit.ly/3Ick3Ec.
If you are interested in learning more about the MOMENTUM Clinical Trial for Patients with Myelofibrosis and determining if your patients may be eligible, please contact a MOMENTUM Trial representative by visiting momentumtrial.com/for-physicians
Triplet Combination Demonstrates Promise for Frontline Treatment of BRAF V600E–mutant CRC

by BRITTANY LOVELY

DOUBLET AND TRIPLET CHEMOTHERAPY-BASED therapies are standard treatment options for patients with BRAF V600–mutant metastatic colorectal cancer (mCRC), although this population of patients have traditionally poor outcomes with chemotherapy-based regimens. Additionally, BRAF inhibitors alone are not effective enough to overcome the feedback activation of EGFR (FIGURE).1

Investigators of the ANCHOR-CRC trial (NCT03693170) hypothesized that targeting multiple nodes in the MAPK pathway may elicit better responses for patients and fill an urgent unmet need for patients whose disease harbors BRAF V600 mutations.2 Specifically, the study was designed to examine the efficacy of the triplet combination of encorafenib (Braftovi), binimetinib (Mektovi), and cetuximab (Erbitux) in the first-line setting.

Updated data analysis presented at the 2021 European Society of Medical Oncology Virtual World Congress on Gastrointestinal Cancer demonstrated that the trial met its primary end point of observed confirmed objective response rate (cORR). In total, 92 patients were evaluable, and the investigator-assessed cORR was 47.8% (95% CI, 37.3%-58.5%); all responses were partial responses for a disease control rate of 88%. Progressive disease was reported in 5.4% of patients.2

The analysis combined 41 patients enrolled to stage 1 of the study with an additional 54 patients enrolled to stage 2. At the time of presentation, 6 patients (15%) from stage 1 and 14 patients (26%) from stage 2 remained on treatment. For the 75 patients who discontinued therapy, the cited reasons included progressive disease (64%), adverse effects (AEs; 21%), investigator decision (8%), and other (7%).

Patients with treatment-naïve mCRC and a confirmed BRAF V600E mutation were treated with oral encorafenib (300 mg daily), oral binimetinib (45 mg orally twice daily), and intravenous cetuximab (400 mg/m2 loading dose, followed by 250 mg/m2 weekly for the first 28 weeks, followed by 500 mg/m2 once every 2 weeks).

At baseline evaluation, the median age was 65 years (range, 30-84) with median time since initial diagnosis of 66 days. Most patients (60%) had right-side or transverse primary tumors and the remaining patients (40%) had either left-side tumors or tumors located in the rectum. In terms of metastases, most patients (75.8%) had more than 2 organs involved, including the liver (54.7%), lymph node (51.6%), peritoneum/omentum (48.4%), and lung (36.8%).

Secondary end points of the study were progression-free survival (PFS), overall survival (OS), safety, quality of life, and pharmacokinetics.

At a median follow-up of 4.8 months, the median PFS was 5.8 months (95% CI, 2.6-6.4) for patients treated with the triplet. At a median follow-up of 14.4 months, the median OS was 17.2 months (95% CI, 14.1-21.1). For 95 patients included in the OS analysis, the OS rates at 12, 18, and 24 months were 65%, 49%, and 29%, respectively.

Investigators noted that most patients were able to receive active subsequent therapies. The median time to subsequent therapy was 6.9 months (range, 5.9-8.4). Specifically, 43.2% of patients went on to receive antineoplastic therapy.

**FIGURE.** MAPK Pathway Inhibition With Triplet Regimen

The triplet regimen of encorafenib, binimetinib, and cetuximab was investigated to provide the most effective inhibition of the MAPK pathway. EGFR-mediated adaptive feedback historically limited the efficacy of single and dual BRAF and MEK inhibition in BRAF V600E–mutant colorectal cancer.
therapy of either oxaliplatin-based doublet with or without bevacizumab (Avastin), FOLFOXIRI with or without bevacizumab, or immunotherapy.

In terms of safety, the results reported for the triplet combination were similar with those reported for recommended chemotherapy-based regimens. The most common all-grade AEs were diarrhea (67.4%), nausea (45.3%), dermatitis acneiform (40.0%), rash (40.0%), and vomiting (37.9%). The most common grade 3 or higher AEs were anemia (10.5%), increased lipase levels (10.5%), diarrhea (9.5%), and nausea (8.4%).

Further, the most frequent serious AEs of grade 3 or higher were intestinal obstruction (14.7%), renal failure (7.4%), nausea (5.3%), and abdominal pain (4.2%). Investigators also noted no meaningful changes in patient-reported outcomes.

Eric Van Cutsem, MD, PhD, who reported the data at the conference, noted that these results were “encouraging” and “support exploring the combination of encorafenib plus cetuximab with chemotherapy in the first-line setting.” Van Cutsem is the division head of clinical digestive oncology at University of Leuven and University Hospitals Gasthuisberg, Leuven, Belgium.

Investigators of the ongoing BREAKWATER study (NCT04607421) will evaluate the efficacy of encorafenib plus cetuximab with or without FOLFOX or FOLFIRI vs the control of physician’s choice of either FOLFOX, FOLFIRI, FOLFOXIRI, or CAPEOX with or without anti-VEGF therapy. Patients who received prior systemic therapy in the metastatic setting are not eligible for enrollment. The primary end points of the study are PFS for arm A vs control and arm B vs control by blinded independent central review. Key secondary end points are OS for arm A vs control and arm B vs control. Other end points include incidence of dose-limited toxicities, AEs, dose modifications, and drug-drug interactions.²³

In April 2020, the combination of encorafenib and cetuximab was approved for the treatment of patients with mCRC with a confirmed BRAF V600E mutation who experienced disease progression after 1 or 2 prior lines of therapy based on results of the BEACON CRC trial (NCT02928224).⁴ Investigators of the trial examined outcomes of the doublet regimen as well as the triplet regimen of encorafenib, binimetinib, and cetuximab against the control of investigators’ choice of either cetuximab and irinotecan or cetuximab and FOLFIRI.

Although the triplet combination group outperformed the doublet therapy group against the control arm, the trial was not powered to compare the 2 arms.¹

For a full list of references, see the article at bit.ly/3lWGkPk.
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION. 1,2 *

Approved across 5 indications spanning a wide range of multiple myeloma patients

INDICATIONS
DARZALEX FASPRO™ is indicated for the treatment of adult patients with multiple myeloma:
• in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
• in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
• in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
• as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation.

WARNINGS AND PRECAUTIONS
Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO™ as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO™ administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO™. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO™ depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
DARZALEX™: For a strong start to their treatment journey

Get the latest data and information at darzalexhcp.com/faspro

Contact your Oncology Specialist to learn more about DARZALEX FASPRO™

~3 to 5 minute administration
• Subcutaneous injection is substantially faster than intravenous daratumumab1,2

The recommended dose of DARZALEX FASPRO™ is 1,800 mg daratumumab and 30,000 units hyaluronidase administered subcutaneously over ~3 to 5 minutes. DARZALEX FASPRO™ is for subcutaneous use only. Do not administer intravenously.

See the Dosage and Administration section of the Prescribing Information for dosing considerations and dosing schedules for approved regimens.

See Important Safety Information below for hypersensitivity and administration reactions, pre-medication and post-medication requirements, and other important considerations for use of DARZALEX FASPRO™.

Efficacy consistent with intravenous daratumumab
• DARZALEX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs Intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients1
  – ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259)*
  – Eligible patients were required to have relapsed or refractory multiple myeloma who had received ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent1

• In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with lenalidomide and dexamethasone (Drd) was evaluated in 65 patients with multiple myeloma who had received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%)

• In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%)

Fewer systemic ARRs vs intravenous daratumumab
• Nearly 3x reduction in systemic administration-related reactions1 (ARRs) with DARZALEX FASPRO™ vs intravenous daratumumab observed in the COLUMBA trial (13% of patients on DARZALEX FASPRO™ had a systemic ARR of any grade vs 34% with intravenous daratumumab)1,3

• Both systemic ARRs, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO™. See Important Safety Information for more details1

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

Thrombocytopenia
Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of platelets.

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

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

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab binding to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO™, type and screen patients prior to starting DARZALEX FASPRO™.

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

ADVERSE REACTIONS
The most common adverse reaction (≥20%) with DARZALEX FASPRO™ monotherapy is: upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia.

The most common hematologic laboratory abnormalities (≥40%) with DARZALEX FASPRO™ are: decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Please see Brief Summary on adjacent pages.


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Daratumumab (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE
Darzalex FASPRO is indicated for the treatment of adult patients with multiple myeloma:
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone in newly diagnosed patients
- in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions
Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO.

Systemic Reactions
In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 3 or 4, Grade 2.1%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 2 minutes to 3.5 days). Of the 94 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids (see Dosage and Administration (2.3) in Full Prescribing Information). Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions (see Dosage and Administration (2.3) in Full Prescribing Information).

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions were observed in >5% of patients. The adverse reaction resulting in injection site erythema was injection site erythema. These local reactions occurred in 0.6% of patients with daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum (see References). The determination of a patient’s ABO and Rh blood type are not impacted (see Drug Interactions).

Hypersensitivity and Other Administration Reactions
In this pooled safety population, injection-site reactions occurred in 4.5% of patients. The adverse reaction resulting in delayed systemic administration-related reaction occurred in 0.6% of patients.

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

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

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause death of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 5 months after the last dose (see Use in Specific Populations). The combination of DARZALEX FASPRO with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

Hypersensitivity and Other Administration Reactions
Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see Drug Interactions). This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Hypersensitivity and Other Administration Reactions (see Warning and Precautions).
- Neutropenia (see Warning and Precautions).
- Thrombocytopenia (see Warning and Precautions).

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

In combination with bortezomib, melphalan and prednisone
The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES (see Clinical Studies [14.1] in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in 5% of patients included pneumonia and pyrexia. Fetal adverse reactions occurred in 3.0% of patients.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>15</td>
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DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj) injection

**Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
<td>3*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral*</td>
<td>13</td>
<td>1*</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
<td>1*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughf</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
<td>3*</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
<td>3*</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1*</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>6*</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>3*</td>
</tr>
</tbody>
</table>

* Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

- Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.
- Abdominal pain includes abdominal pain, and abdominal pain upper.
- Fatigue includes asthenia, and fatigue.
- Edema peripheral includes edema, edema peripheral, and peripheral swelling.
- Cough includes cough, and productive cough.

**Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisonea</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-VMP (N=67).
Darazalex Faspro™ (Daratumumab and Hyaluronidase-fihj) Injection

- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain
- Nervous system disorders: dizziness, headache, paresthesia
- Skin and subcutaneous tissue disorders: rash, pruritus
- Gastrointestinal disorders: abdominal pain
- Infections: influenza, sepsis, herpes zoster
- Metabolism and nutrition disorders: decreased appetite
- Cardiac disorders: atrial fibrillation
- General disorders and administration site conditions: chills, infusion reaction, injection site reaction
- Vascular disorders: hypotension, hypertension

Table 4 summarizes the laboratory abnormalities in patients who received Darazalex Faspro with Lenalidomide and dexamethasone (D-Rd) in PLEIADIES.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Darazalex Faspro with Lenalidomide and Dexamethasone&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td></td>
<td>94</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with D-Rd (N=65).

Monotherapy

The safety of Darazalex Faspro as monotherapy was evaluated in COLUMBA (see Clinical Trials (14.2) in Full Prescribing Information). Patients received Darazalex Faspro 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks after week 24. The following adverse reactions have been identified with use of intravenous daratumumab and hyaluronidase products or other hyaluronidase products may be misleading.

- Respiratory, thoracic and mediastinal disorders: pulmonary edema

Table 5 summarizes the adverse reactions in COLUMBA.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Darazalex Faspro (N=258)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades ≥3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24 1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>22 1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infusion reactions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>34 5&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

Monotherapy

Clinical relevant adverse reactions in <10% of patients who received Darazalex Faspro include:

- General disorders and administration site conditions: injection site reaction, peripheral edema
- Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal chest pain, muscle spasms
- Gastrointestinal disorders: constipation, vomiting, abdominal pain, hypocalcemia, dehydration
- Cardiac disorders: hypertension, hypotension
- Respiratory, thoracic and mediastinal disorders: pulmonary edema, hypotension
- Vascular disorders: hypertension
- Infections: bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B reactivation
- Skin and subcutaneous tissue disorders: pruritus, rash

Table 6 summarizes the laboratory abnormalities in COLUMBA.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intravenous Daratumumab&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3–4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>65 19 57 14</td>
<td>65 19 57 14</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>59 36 56 36</td>
<td>59 36 56 36</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>55 10 43 11</td>
<td>55 10 43 11</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>43 16 45 14</td>
<td>43 16 45 14</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42 14 39 16</td>
<td>42 14 39 16</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of 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 daratumumab products or other hyaluronidase products may be misleading.

Treatment-emergent anti-daratumumab antibodies were tested in 451 patients treated with DARZALEX FASPRO as monotherapy or as part of a combination therapy. One patient (0.2%) who received DARZALEX FASPRO tested positive for anti-daratumumab antibodies and transient neutralizing antibodies. However, the incidence of antibody development might not have been reliably determined because the assays that were used have limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab.

Treatment-emergent anti-rHuPH20 antibodies developed in 8% (19/255) of patients who received DARZALEX FASPRO as monotherapy and in 8% (16/192) of patients who received DARZALEX FASPRO as part of combination therapy. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposures. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

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

- Immune System: Anaphylactic reaction
  - Gastrointestinal: Pancreatitis
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fhij) injection

DRUG INTERACTIONS
Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)
Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding [see References] or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models [see Data]. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse neonatal or fetal outcomes. Animal reproduction studies have not been conducted.

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 outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of DARZALEX FASPRO and lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Lenalidomide is only available through a REMS program. Refer to the lenalidomide prescribing information for use during pregnancy.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab in utero until a hematologic evaluation is completed.

Data

Animal Data
DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 6 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs). No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 980,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Animal Data
No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 980,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

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

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

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

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

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

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

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

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

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Novel Compound Looks to Shake Up mCRPC Treatment Landscape

by BRITTANY LOVELY

ANDROGEN DEPRIVATION THERAPY serves as the first-line treatment option for patients with metastatic prostate cancer; however, disease progression typically occurs within 1 to 2 years of hormonal therapy. Data have shown that androgen receptor–targeting agents including enzalutamide (Xtandi), abiraterone acetate (Zytiga)/prednisone, darolutamide (Nubeqa), and apalutamide (Erleada) have elicited response for patients with metastatic castration-resistant prostate cancer (mCRPC), but approximately 75% of patients progress and up to 25% do not respond to initial therapy.

The need for safe and effective therapeutic options prior to the initiation of chemotherapy remains an unmet need in the treatment landscape. To that end, investigators have commenced a phase 3 study of sabizabulin (VERU-111) for the treatment of patients with mCRPC who have failed prior treatment with at least 1 androgen receptor–targeting agent.

“Whatever we always find tough when we’re designing these studies is that we have a number of different agents to treat mCRPC, but it’s always difficult when we think about sequencing those agents,” Mark Christopher Markowski, MD, PhD, said in an interview with OncologyLive®. Markowski is an assistant professor of oncology at Johns Hopkins University School of Medicine in Baltimore, Maryland.

The discovery of an agent with a unique mechanism of action led investigators to examine sabizabulin, an oral therapy that binds to the colchicine binding site on the microtubule to crosslink α and β tubulin and inhibits microtubule polymerization.

“What do you put a compound like this in the treatment paradigm?” Markowski asked. “I think it is always challenging, and what we’ve come up with here is that we’d like to target [the use of] this agent after some of the oral androgen targeted therapies,” he said. “If [a patient has] progressed on abiraterone, then maybe this is a compound for [them]. I think if we have to think about the future [that] this compound is maybe a way to delay taxane chemotherapy.”

The VERACITY trial (NCT04844749) will evaluate the novel small molecule against available alternate androgen receptor–targeting agents including enzalutamide, abiraterone/prednisone, darolutamide, and apalutamide. Eligible patients with rising prostate-specific antigen (PSA) levels and tumor progression while receiving androgen receptor–targeting therapy will be randomized 2:1 (FIGURE 1).

“We’re going to recruit approximately 250 [patients] at a number of different sites. We’re going to look at radiographic progression-free survival [rPFS] as our end point, and hopefully, once the study is fully enrolled and we start getting data, we’ll have a positive result,” Markowski said.

THE PATH TO PHASE 3

The initiation of the trial follows demonstrated antitumor activity and a favorable safety with the agent observed in data from the phase 1b expansion cohort and the population enrolled in the phase 2 evaluation of the recommended dose. Markowski presented updated data on the study as part of the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting in June. In their conclusions, the authors of the poster noted that sabizabulin was “well tolerated with no reports of significant neutropenia or neurotoxicity” and that “daily chronic drug administration [was] feasible and safe.”

In the phase 1b component of the study, investigators leveraged a 3 + 3 design, escalating the dosage of oral sabizabulin 4.5 mg to 81 mg over 21-day cycles (7 days on drug, followed by 14 days off). The expansion cohort of the trial used a continuous dosing schedule similar to that used in the phase 2 portion, in which the recommended phase 2 dose of 63 mg daily was used.

Efficacy for the 30 patients enrolled in the phase 1b portion was assessed by PSA level and bone/CT scans. For the 10 patients who received at least 4 continuous 21-day cycles of treatment, 60% had reported PSA declines, with 40% of patients

![Mark Christopher Markowski, MD, PhD](image)
reporting a decline of at least 30% and 20% reporting a decline of at least 50% compared with baseline PSA levels.

At the time of presentation at 2021 ASCO, the median rPFS was 12.4 months in those who received sabizabulin at a dose of at least 63 mg. The phase 2 portion of the trial is ongoing, with investigators reporting that some patients have remained on study for more than 9 months, objective tumor responses have been observed and include complete and partial responses, and some patients have had PSA decreases greater than 50%.

A combined analysis of the patients from both portions of the study who received at least the recommended 63-mg dose was also reported. In the intention-to-treat population (n = 29), the objective response rate was 20.7% and comprised 5 partial responses and 1 complete response. This rate of response was slightly improved in an analysis of 26 patients who would qualify for enrollment in the phase 3 study at 23.1%.4

“I think the most important part is the safety profile,” Markowski said. “The mechanism of the drug, it’s a microtubule or polymerization inhibitor, and we wanted to see what the toxicity profile of the [sabizabulin] compound looked like compared with taxane chemotherapies.”

In an analysis of the most prevalent adverse effects (AEs) from patients treated with the 63-mg dose of sabizabulin across the phase 1b and 2 studies (n = 54), the most commonly reported all-grade AEs included diarrhea (59.3%), fatigue (33.3%), nausea (31.5%), and decreased appetite (31.5%).5 In terms of diarrhea, 88% of the reported incidents were grade 1 and 2 and medically manageable. “Most of the [AEs] that we saw were GI [gastrointestinal] related—nausea, some diarrhea—and they were low grade and easily manageable with oral medicines or just stopping the drug,” Markowski added.

Investigators noted that they anticipate diarrhea to occur less in the phase 3 study because of better oral bioavailability of the phase 3 dosage formulation, which should result in reduced exposure of nonabsorbed sabizabulin to the gastrointestinal tract.5

**THE FUTURE OF SABIZABULIN FOR mCRPC**

Of note in the efficacy data, at the time of presentation, the median PFS was 12 months (95% CI, 6-23+), with 3 patients continuing on study, 2 of whom have been on study for approximately 2 years.5

“We are seeing durable disease stability, and I think that was a bit of a surprise,” Markowski said. “Many patients on the study, maybe they didn’t achieve a 30% decrease in their tumor volume, but they certainly didn’t have disease progression, and they’ve [remained] on the study for a long time. We’re really seeing nice durable effects, and I think that’s what we’re trying to emphasize here.”

“We have to think about the future, and this compound is a way to maybe delay taxane chemotherapy.”

—MARK CHRISTOPHER MARKOWSKI, MD, PhD

**VERACITY investigators hypothesize**

that the median rPFS will double for those treated with sabizabulin at approximately 7.4 months vs 3.7 months for those randomized to receive an alternative androgen receptor–targeting agent. Secondary end points of the trial include objective response rate, duration of objective response, interim analysis of overall survival, time to intravenous chemotherapy, and pain progression.3,5

Investigators also plan to stratify patients by measurable disease vs bone-only disease and if the patient has failed 1 vs more than 1 prior androgen receptor–targeting agent. They anticipate that a significant proportion (> 30%) of patients randomized into the study will have measurable disease at baseline.3

As the phase 3 trial rolls out, Markowski reflected on the available data and concluded, “I think that hopefully we’re going to put [sabizabulin] on individuals’ radar. As we move forward with the phase 3 [trial], investigators are going to be looking for [these] data [and asking], ‘Is this a viable option for prostate cancer? And I think the answer is ‘yes.’ ”

**VERACITY is actively enrolling patients across 40 sites in the US.**

**REFERENCES**


To decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen

SPARE THE MARROW. COSELA HELPS PROTECT AGAINST MYELOSUPPRESSION,

**COSELA™ (trilaciclib) helps protect hematopoietic stem and progenitor cells (HSPCs), the source of blood cell lineages**

PROACTIVELY HELP PROTECT AGAINST MULTIPLE MYELOSUPPRESSIVE CONSEQUENCES WITH THE FIRST AND ONLY MYELOPROTECTION THERAPY

The Pivotal Study (Study 1) compared an etoposide/carboplatin + atezolizumab (E/P/A) regimen with COSELA vs without COSELA*.

**INDICATION**

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

*COSELA was evaluated in 3 randomized, double-blind, placebo-controlled clinical studies. The Pivotal Study (Study 1) evaluated COSELA or placebo administered prior to treatment with E/P/A in 107 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. In this study, COSELA significantly reduced the primary endpoints of incidence (adjusted relative risk [aRR] 0.038 [95% CI, 0.008, 0.195], P<0.0001) and duration in Cycle 1 (mean difference -3.6 [95% CI, -4.9, -2.3], P=0.0001) of severe neutropenia and significantly decreased the rate of all-cause chemotherapy dose reductions (aRR 0.242 [95% CI, 0.079, 0.742]). The incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks were 13% and 21% (aRR 0.642 [95% CI, 0.294, 1.404]) with and without COSELA, respectively.
SPARE THE MARROW.
WHILE CHEMOTHERAPY TARGETS CANCER CELLS

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATION
- COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

WARNINGS AND PRECAUTIONS

Injection-Site Reactions, Including Phlebitis and Thrombophlebitis
- COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) adverse reactions. Monitor patients for signs and symptoms of injection-site reactions, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA. Injection-site reactions led to discontinuation of treatment in 3 (1%) of the 272 patients.

Acute Drug Hypersensitivity Reactions
- COSELA administration can cause acute drug hypersensitivity reactions, which occurred in 16 (6%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

Interstitial Lung Disease/Pneumonitis
- Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 1 (0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

Embryo-Fetal Toxicity
- Based on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

ADVERSE REACTIONS
- The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-GITX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.
COSELA™ (trilaciclib) for injection, for intravenous use

Initial U.S. Approval: 2021

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult women with advanced or metastatic solid tumors who are scheduled to receive a platinum-containing regimen or a taxane-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

DOSAGE AND ADMINISTRATION
Recommended Dosage
The recommended dose of COSELA is 240 mg/m² per dose. Administer as a 30-minute intravenous infusion administered within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.

The interval between doses of COSELA as sequential treatments should not be greater than 28 days. Sequential treatments are defined as:

- If the COSELA dose is missed, discontinue chemotherapy on the day the COSELA dose was missed. Consider resuming both COSELA and chemotherapy on the next scheduled day for chemotherapy.
- If COSELA is discontinued, wait 96 hours from the last dose of COSELA before resuming chemotherapy.

Dose Modification for Adverse Reactions
Without discontinuation, or after the administration of COSELA to manage adverse reactions as described in Table 1, reduce COSELA as indicated and proceed with subsequent infusions.

Table 1: Recommended Actions for Adverse Reactions

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Acute drug hypersensitivity reactions

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Other toxicities

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Intensive care unit admissions

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ASCO Roadmap Provides Path Forward for Clinician Well-Being

by BRITTANY LOVELY

EDUCATIONAL PROGRAMS AIMED AT implementing systemic-level changes may provide oncology care providers with the necessary tools to mitigate the increasing prevalence of burnout. A collaborative initiative between the American Society of Clinical Oncology (ASCO) and the American Medical Association (AMA) has the goal of improving well-being and reducing burnout by leveraging a quality improvement framework and model.1

Approximately 45% of medical oncologists who are members of ASCO have reported symptoms associated with burnout, including emotional exhaustion or depersonalization. Classified as an occupational-related condition by the World Health Organization, the most recent definition of burnout results from unaddressed chronic workplace-related stress.2

Turnover and early retirement are 2 consequences associated with burnout with organizational contributors being cited as the source of the problem. Circumstances specific to the oncology care space include exposure to patients and families in crisis during any point of the treatment process, ethically challenging situations, and potentially repeated encounters with limited treatment options and treatment failure (FIGURE1).

“Many institutions and organizations across the country are realizing that burnout amongst clinicians is a true and serious phenomenon,” Piyush Srivastava, MD, said in a virtual presentation during the 2021 ASCO Annual Meeting. Srivastava is an oncologist at Kaiser Permanente Medical Group’s Walnut Creek Medical Center in California. “For many of us and for many of our employers, simply acknowledging that this is an issue affecting us as healthcare providers [is important] and [can lead to the] creation of an environment to address this awareness with intentional actions to address the problem.”

In a discussion of oncology care well-being, Srivastava noted 3 domains of influence that are essential to wellness: personal resilience, a culture of awareness, and efficiency of practice.

“Personal resilience [in this instance, refers to] the ability to individually cope with loss and grief and stress and the techniques typically used to aid in the coping,” he said. “A second domain is creating a culture of awareness or, specifically, individual and systemic factors established for well-being. And a third is efficiency of practice—or removing the pebbles in our shoes, which get in the way of taking care of our patients. Mostly, these are operational barriers.”

To address system barriers mitigating clinician well-being and increasing burnout, a quality training program focuses on providing training to oncology providers giving them the tools to design, implement, and lead successful quality improvement activities, with the goal of implementing initiatives at their institutions. Specifically, Srivastava discussed the ASCO quality training program, a 6-month comprehensive education and training initiative for multidisciplinary oncology teams.1

“The AMA provided burnout assessments to be used to measure baseline [stress] and to measure the possible affect tested solutions made,” he said. Additionally, the AMA aided in the evaluation of results, creating detailed reports of the findings. “ASCO faculty and coaches worked together to provide the knowledge base for quality...”

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Piyush Srivastava, MD
improvement and guide the teams [toward] viable solutions.”

**TRAINING LAYS THE GROUNDWORK FOR CHANGE**

Launched in 2019, the first ASCO quality training program centered on improving efficiency in practices. Teams focused on identifying systemic challenges that affect well-being and developed tactics to address these hurdles. Strategies were aimed at reductions in workload, increased patient-physician interaction and enhanced autonomy, with the goal of favorably affecting physician burnout.2

As part of the program’s design, the in-person and virtual training sessions provide interaction with improvement coaches, with opportunities for simulation exercises. The program is divided into 4 phases: prework, planning, implementation, and sustain/spread. A key component of the final phase according to Srivastava is the presentation of a plan to sustain developed solutions and collect data from these initiatives for continuous improvement.

“The [in-person] sessions for thematic burnout mitigation included interactive lectures developed by experts in quality improvement, physician wellness, and burnout with team-building activities, discussion and presentation of case examples, small group exercises addressing physician wellness and mitigating burnout, and presentations by each practice team of their plan,” Srivastava said.

The results of the quality training program provide a blueprint for key stakeholders to implement organization interventions. Objectives were divided into cognitive, affective, and psychomotor categories.

“For the cognitive or knowledge-based objectives, teams wanted to identify clinical and operational targets for practice improvement, but they also wanted to demonstrate understanding of how to use process analysis tools to improve on that, as well as describe and discuss effective approaches to engage their local stakeholders to improve practice efficiency,” Srivastava said.

Psychomotor objectives focused on developing strategic plans for operational performance improvements using data collected from tracking performance over time. The implementation of these tactics relied on the engagement of local stakeholders and leaders to support wellness activities.

**THE ASCO ROADMAP**

Although interventions aimed at addressing the root problems that enable burnout have been proven effective,3 dissemination of information, education, and reduction of stigma associated with mental health and burnout.

The 6-month training initiative builds on the increased efforts to bring light the burdens affecting oncology practices from the ASCO Oncology Clinician Well-Being Task Force and includes a roadmap that provides a 5-year, goal-orientated mission to provide sustainable practices. The 3 goals of the program focus on improving the quality of cancer care through efforts that address an individual’s work-related and personal health-related environment, including organizational and psychosocial factors.4

The first aim of the organization is to engage clinician well-being across ASCO activities, which includes promotion of educational and policy solutions as well as incorporating well-being initiatives in volunteer and professional development programs. The second goal focuses on addressing diversity, equity, and inclusion boundaries to broaden and diversify oncology clinician resources. The final goal centers on the promotion of research that highlights the understanding of oncology clinician well-being through the publishing and dissemination of information on burnout.4

“I believe that one of the biggest successes for the quality training program on burnout was the awareness of burnout as a real entity and the start of conversations addressing this as a real issue plaguing the oncology workforce,” Srivastava said.

**REFERENCES**


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LAKSHMI NAYAK, MD, is director of the Center for Central Nervous System Lymphoma at Dana-Farber Cancer Institute and an assistant professor of neurology at Harvard Medical School in Boston, Massachusetts.

**PRIMARY CENTRAL NERVOUS SYSTEM lymphoma (PCNSL)** is a rare and aggressive variant of extranodal non-Hodgkin lymphoma (NHL) that occurs in the brain, spinal cord, cerebrospinal fluid (CSF), or eyes in the absence of systemic disease. Although it responds favorably to chemotherapy and radiation, prognosis is inferior to that of other subtypes of NHL. PCNSL accounts for 3% of all brain tumors and 6% of all extranodal lymphomas, and approximately 90% of cases are classified as diffuse large B-cell lymphomas (DLBCLs), with T-cell lymphoma, low-grade lymphoma, and Burkitt lymphoma accounting for the remaining 10%. Histopathology reveals malignant B cells in an angiocentric pattern with diffuse infiltration of the central nervous system (CNS), indistinguishable from systemic DLBCL, and gene-expression profiling demonstrates that the majority of PCNSLs are of the nongerminial center or activated B-cell-like (ABC) subtype. Age and performance status have been identified as independent predictors associated with prognosis. An early diagnosis by brain biopsy is preferable, followed by an evaluation of the extent of disease for staging and rapid institution of treatment; these are paramount to achieve neurologic recovery and improve survival.

Management of newly diagnosed PCNSL has evolved over the past several years and standard-of-care guidelines are based on data from both single-arm and randomized phase 2/3 trials. In general, high-dose methotrexate (HD-MTX) in combination with an alkylating agent, such as high-dose cytarabine and rituximab (Rituxan), is recommended for induction therapy, although the role of rituximab, particularly in elderly patients, is the focus of debate because of conflicting trial results. The majority of HD-MTX-based chemotherapy regimens have demonstrated complete response rates of 50% and overall response rates of up to 90%. Intrathecal chemotherapy is not utilized based on data from prior studies and only offered to patients with an insufficient CSF response to HD-MTX or to those who are unable to receive HD-MTX at a dose of at least 3 g/m², which is required for adequate CSF penetration.

It is unclear whether patients with ocular involvement would benefit from the addition of local therapy in the form of intravitreal MTX or ocular radiation to systemic chemotherapy. Typically, local therapy is considered if systemic therapy fails to achieve ocular disease control or if there is ocular recurrence. Consolidation therapy is recommended after completion of induction in appropriate patients to improve long-term disease-free survival. Whole-brain radiation therapy (WBRT) has historically been used for consolidation; however, there is increasing evidence that WBRT results in delayed and irreversible neurocognitive impairment in patients who are 60 years or older, particularly when delivered in combination with HD-MTX. Given that the median age when receiving a diagnosis is 65 years, this approach is no longer preferred as first-line treatment and is reserved for salvage. Reduced-dose WBRT is under investigation in a randomized clinical trial.

**DETERMINING THE RIGHT TREATMENT REGIMEN**

Although there is a progression-free survival (PFS) benefit, the impact on long-term neurotoxicity remains to be seen. Over the past 10 years, long-term results of studies with high-dose chemotherapy followed by autologous stem cell transplant (HDC-ASCT) have demonstrated encouraging long-term PFS and overall survival (OS). Five-year PFS and OS rates of 81% to 83% have been reported specifically with thiotepa-based conditioning regimens, which are recommended over other conditioning regimens such as BEAM (carmustine, etoposide, cytarabine, and melphalan) or CBV (cyclophosphamide, carmustine, and etoposide), which have led to inferior outcomes.

Data from 2 European, multicenter, randomized studies (NCT01011920, NCT00863460) comparing WBRT and HDC-ASCT for consolidation have shown similar efficacy or slight improvement of outcomes on the ASCT arm. Importantly, both studies note improvement of neurocognitive function with ASCT and worsening with WBRT. However, many studies investigating the role of HDC-ASCT have included younger, healthier patients. Additionally, the treatment-associated mortality with ASCT has been variable, ranging from 0% to 14%. Although this approach remains attractive, it requires careful patient selection and treatment at a specialized center. Overall, fewer than 10% to 15% of patients are candidates for such therapy.

Nonmyeloablative chemotherapy regimens are also being considered for consolidation as an alternative to ASCT. Initial studies with high-dose etoposide and cytarabine (EA) have demonstrated encouraging results. Recent results from a randomized phase 2 study (NCT01511562), which compared EA with HDC-ASCT after induction plus MTR-A (HD-MTX, temozolomide [Temodar], rituximab,
cytarabine) and was conducted by Alliance for Clinical Trials in Oncology, demonstrated superior PFS with ASCT; however, there was a notable difference in progressors (28% vs 11%, respectively; \( P = .05 \)) during induction, which was the same treatment on both arms.\(^\text{19}\) There was no significant difference in OS.

**OVERCOMING ROADBLOCKS FOR THE ELDERLY POPULATION**

The improvement of treatment regimens for PCNSL has resulted in doubling of outcomes in patients over the past 2 decades, although survival in elderly patients has not changed since the 1970s.\(^\text{20}\) This is likely multifactorial. Older age has shown to be an independently adverse prognostic factor, regardless of treatment, and these patients, who account for a significant number of patients with PCNSL, typically have multiple comorbidities and cannot tolerate the aggressive regimens previously described.

Recent data from tertiary care institutions and experienced groups have shown that HD-MTX regimens can be delivered safely in elderly patients and can lead to clinical meaningful outcomes.\(^\text{21}\) In patients who are unable to safely tolerate and clear HD-MTX due to tentative renal function, such as many older patients, glucarpidase can be used to cleave MTX into nontoxic metabolites eliminated by the liver.\(^\text{22}\) There are ongoing clinical trials in several cancers, including PCNSL, to determine if glucarpidase can be used to safely deliver HD-MTX as an outpatient therapy to eliminate the long hospital stays required for continuous intravenous hydration. Consolidation options in older patients are currently lacking.

**BIOMARKERS COULD BE THE FUTURE OF CARE**

Up to one-third of patients with PCNSL are refractory to first-line therapy, and approximately 50% have a recurrence in the first 2 years.\(^\text{23}\) The management of relapsed or refractory disease is challenging because of limited treatment options and factors such as age and further neurologic impairment. Recent insights into the pathophysiology of PCNSL have led to its recognition as a biologically distinct disease with targetable alterations and mutations.

B-cell receptor (BCR) has been identified as a key signaling pathway in PCNSL. Frequent genetic alterations of NF-κB and components of the toll-like receptor (TLR), such as MYD88 and the proximal BCR such as CD79B, are seen in PCNSL in higher percentages (>70%-80%) compared with the ABC subtype of systemic DLBCL.\(^\text{24,25}\) Deletions or mutations in TNFAIP3 associated with chromosome 6q loss have been noted, as have chromosome 18q gains with high BCL2 expression. Copy number amplifications at chromosome 9p24.1 associated with PD-L1/PD-L2 expression have been described, which may imply a role in immune evasion in PCNSL. These and other observations have led to several phase 1 and 2 clinical trials with novel targeted agents as well as immunotherapies (TABLE\(^\text{24,27-34}\)).

**TABLE. Targeted Agents in CNS Lymphoma\(^\text{24,27-34}\)**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial identifier (phase)</th>
<th>Number of patients</th>
<th>ORR (95% CI)</th>
<th>mPFS, months (95% CI)</th>
<th>mOS, months (95% CI)</th>
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<tbody>
<tr>
<td>Temsirolimus</td>
<td>NCT00942747 (1)</td>
<td>37</td>
<td>54% (37%-71%)</td>
<td>2.1 (1.1-3.0)</td>
<td>3.7 (1.5-5.8)</td>
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<tr>
<td>Ibrutinib</td>
<td>NCT02315326 (1/2)</td>
<td>13 (PCNSL cohort)</td>
<td>77% (56%-94%)</td>
<td>4.6 (2.4-7.5)</td>
<td>15 (NA)</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>NCT02542514 (2)</td>
<td>44*</td>
<td>52%</td>
<td>4.8 (2.8-12.7)</td>
<td>19.2 (7.2-NA)</td>
</tr>
<tr>
<td>Ibrutinib monotherapy followed by ibritnib plus chemotherapy</td>
<td>NCT02203526 (1)</td>
<td>14</td>
<td>86% (57%-98%)</td>
<td>15.3 (1.3-undefined)</td>
<td>NR; 53% (21.4%-74.9%) of patients alive at 1 year</td>
</tr>
<tr>
<td>Ibrutinib with high-dose methotrexate plus rituximab</td>
<td>NCT02315326 (1)</td>
<td>9</td>
<td>89% (52%-100%)</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Tirabrutinib</td>
<td>JapicCTI-173646 (1/2)</td>
<td>44</td>
<td>63.6% (47.8%-77.6%)</td>
<td>2.9 (1.8-11.1)</td>
<td>NR</td>
</tr>
<tr>
<td>Rituximab/lenalidomide</td>
<td>NCT01956695 (2)</td>
<td>45</td>
<td>35.6% (21.9%-51.2%)</td>
<td>7.8 (3.9-11.3)</td>
<td>17.7 (12.9-NA)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>NCT01722305 (1)</td>
<td>25</td>
<td>48% (27.8%-68.7%)</td>
<td>5.3 (3.7-16.6)</td>
<td>NA</td>
</tr>
</tbody>
</table>

CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NR, not reached; ORR, overall response rate. *Intention-to-treat population included patients with relapsed or refractory DLBCL-PCNSL or primary vitreoretinal lymphoma.
INDICATIONS
Retevmo is a kinase inhibitor indicated for the treatment of:
• adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
• adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
• adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

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

<table>
<thead>
<tr>
<th>Treatment naïve (n=39)</th>
<th>Previously treated with platinum chemotherapy (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 54, 73)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>1.9% CR + 62% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR was 17.5 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE)</td>
<td>(95% CI: 12, NE)</td>
</tr>
<tr>
<td>median follow-up: 7.4 months&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>median follow-up: 12.1 months&lt;sup&gt;1,5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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

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

---

**Adverse Reactions and Laboratory Abnormalities**

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

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

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

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

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**Find RET. Find results on Retevmo.com.**

**Trial Design** The phase I/II, multicohort, open-label, single-arm, multicenter LIBRETTO-001 trial evaluated the efficacy of Retevmo in a population of 702 patients with metastatic RET fusion-positive NSCLC (n=332), advanced or metastatic RET fusion-positive thyroid cancer (non-MTC) (n=38), advanced or metastatic RET-mutant MTC (n=306), and certain other advanced solid tumors with RET alterations (n=26). The study enrolled the following cohorts: systemic therapy-naive patients (n=39) and previously treated (n=105) patients who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC; systemic therapy-naive (n=8) and previously treated (n=19) patients with advanced or metastatic RET fusion-positive thyroid cancer (non-MTC); and treatment-naive (n=88) and previously treated (n=55) patients with advanced or metastatic RET-mutant MTC. Major efficacy outcomes were ORR and DoR. In phase II, the dose for Retevmo was 160 mg PO BID.‡‡ ORR was defined as CR + PR and was assessed by independent review committee (IRC) according to RECIST v1.1. All results reviewed by an IRC.<sup>1,5</sup>

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Retevmo can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, hemorrhagic events can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

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

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

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

Severe adverse reactions (Grade 3–4) occurring in >15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspepsia (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

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

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

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

Laboratory abnormalities (all grades; Grade 3–4 ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (43%; 6%), ALT increased (45%; 9%), increased total cholesterol (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%)

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

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

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

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

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

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

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

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

RETEVMO™ (selpercatinib) capsules, for oral use
Initial U.S. Approval: 2020

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

INDICATIONS AND USAGE
RETEVMO (selpercatinib) is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic RET-fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-fusion-positive thyroid cancer who require systemic therapy are radioactive iodine-refractory (if radioactive iodine is inappropriate)

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

CONTRAINDICATIONS:
None

WARNINGS AND PRECAUTIONS

Hepatotoxicity
Serious hepatic adverse reactions occurred in 2.6% of patients treated with RETEVMO. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased ALT occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years).

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

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

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

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

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity.

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

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

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.8%. The median time to onset was 1.7 weeks (range: 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminases.

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

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

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

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

ADVERSE REACTIONS

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

RET Gene Fusion or Gene Mutation Positive Solid Tumors

The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 702 patients in LIBRETTO-001. Among 702 patients who received RETEVMO, 65% were exposed for 6 months or longer and 34% were exposed for greater than one year. Among these patients, 95% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

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

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

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

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

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

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

Table 1 summarizes the adverse reactions in LIBRETTO-001.

Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grades 1-4 (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RETEVMO (n=702)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
<td>3.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>1.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
<td>18</td>
</tr>
</tbody>
</table>

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RETEVMO™ (selpercatinib) capsules, for oral use
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### Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVMO (n=702)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>35</td>
<td>2.0</td>
</tr>
<tr>
<td>Edema*</td>
<td>33</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache*</td>
<td>23</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>16</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Blood and Lymphatic System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>15</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Only includes a grade 3 adverse reaction.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVMO include hypothyroidism (9%).

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

### Table 2: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVMO*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>42</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>41</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>37</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>36</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>24</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Decreased glucose</td>
<td>22</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>33</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

*Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

### DRUG INTERACTIONS

**Effects of Other Drugs on RETEVMO**

**Acid-Reducing Agents**

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

**Strong and Moderate CYP3A Inhibitors**

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

**Strong and Moderate CYP3A Inducers**

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

**Effects of RETEVMO on Other Drugs**

**CYP2C8 and CYP3A Substrates**

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

**Drugs that Prolong QT Interval**

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

### USE IN SPECIFIC POPULATIONS

**Pregnancy**

**Risk Summary**

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

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

**Data**

**Animal Data**

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg (approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily) resulted in 100% post-implantation loss. At the dose of 50 mg/kg (approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily), 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

**Lactation**

**Risk Summary**

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

RETREVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MV2020

RETREVMO™ (selpercatinib) capsules, for oral use

SE HCP BS 08MV2020
Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who

Table 2 summarizes the laboratory abnormalities in LIBRETTO-001.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>43</td>
</tr>
<tr>
<td>Increased bilirubin</td>
<td>23</td>
</tr>
<tr>
<td>Increased potassium</td>
<td>24</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>27</td>
</tr>
<tr>
<td>Increased total cholesterol</td>
<td>31</td>
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<tr>
<td>Increased creatinine</td>
<td>37</td>
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<tr>
<td>Decreased calcium</td>
<td>41</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>44</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
</tr>
<tr>
<td>Increased AST</td>
<td>51</td>
</tr>
</tbody>
</table>

Hematology

Fatigue

General

Headache

Skin

Edema

Investigations

Subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel bleeding, hematemesis, hemorrhagic anemia, intraabdominal hemorrhage, lower gastrointestinal diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, discomfort, gastrointestinal pain

RETEVMO-related adverse reactions in patients with hepatic impairment.

Of 702 patients who received RETEVMO, 34% (239 patients) were ≥ 65 years of age and 10% (67 patients) were > 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥ 65 years of age and younger patients.

Renal Impairment

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

Hepatic Impairment

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

Rx only.

Additional information can be found at www.retevmo.com.
Chemotherapy-Free Strategies Chart a New Course for Ph-Positive ALL

by BRITTANY LOVELY

A NEW ERA FOR PATIENTS with newly diagnosed Philadelphia (Ph) chromosome-positive acute lymphoblastic leukemia (ALL) may be on the horizon as investigative efforts aimed away from chemotherapy-based regimens prove efficacious. The 5-year survival rates for chemotherapy in combination with first-generation or second-generation tyrosine kinase inhibitors (TKIs) range from 35% to 50%; however, acquired T315I mutations are a driving cause of relapse.1 Also known as the “gatekeeper” mutation, T315I increases activity of BCR-ABL mutations; previous efforts with dual inhibitors have limited efficacy and unfavorable safety profiles.2

Two agents are at the forefront of paving the way for improvements for this patient population: the BCR-ABL TKI ponatinib (Iclusig) and the bispecific T-cell engager blinatumomab (Blincyto).1 Based on prior efficacy data in combination with hyper-CVAD (cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone), and as monotherapy options, respectively, the rationale to combine the 2 agents was executed in a phase 2 study (NCT03263572). Investigators presented results at the 2021 American Society of Clinical Oncology Annual Meeting (TABLE). For 20 patients with Ph-positive ALL treated in the frontline setting, 100% had a complete response (CR) to treatment with complete molecular remission (CMR) reported for 85% of patients. No patients treated in the frontline setting went on to hematopoietic stem-cell transplantation. “Ph-positive ALL is very different, and we have to obtain [minimal residual disease] negativity as much as we can with the first-line treatment, so we can’t go wrong,” said moderator Jorge E. Cortes, MD, during a recent edition of OncLive® Leukemia Talk. “I think that’s a key point that we have to address in ALL.” Cortes was joined by Robin Foà, MD; Elias Jabbour, MD; and B. Douglas Smith, MD, for a discussion on how these data may reshape the treatment paradigm for patients with Ph-positive ALL.

CORTES We’ve been moving toward TKI-based therapy in ALL. The first studies introduced imatinib [Gleevec] in combination with hyper-CVAD. Then with second-generation and third-generation agents we started seeing greatly improved survival and patients who would do well even without a transplant—results that we couldn’t get with chemotherapy alone.

However, this abstract [70011] introduces a different concept, which is going away from chemotherapy, not using it—this is almost unthinkable, that you wouldn’t use hyper-CVAD for ALL. This is a no-chemotherapy regimen with ponatinib and blinatumomab, and the results look outstanding.

Dr Jabbour, we have had great experience with hyper-CVAD and ponatinib, efficacy-wise. How do you see those 2 playing against each other?

JABBOUR It’s major progress for us at [The University of Texas] MD Anderson [Cancer Center] to move away from...
hyper-CVAD and to move into a new era [with] the concept of chemotherapy-free treatment, like we did for acute promyelocytic leukemia in the old days with arsenic trioxide. [This treatment would mean] not only moving away from intensive chemotherapy, but also moving away from transplant as well.

To improve outcomes for Ph-positive ALL, 2 things became very important based on observation. Induction of CMR is a must, because if we have CMR we do not need to intensify the treatment. Second is suppression of immersion of T315I mutation, which is quite common among patients who receive TKIs.

Hyper-CVAD plus ponatinib is a very effective therapy, so we thought, ‘If ponatinib is so great, do we still need intensive chemotherapy?’ We also had blinatumomab, a bispecific engager, that has shown activity in Ph-positive ALL in the relapsed or refractory setting. Therefore, we decided to combine these 2 drugs with no chemotherapy.

Patients enrolled in the study received 5 courses of blinatumomab, 4 weeks on, 2 weeks off, and ponatinib with a starting dose of 30 mg per day continuously with reduction to 15 mg once CMR was obtained. We started blinatumomab from day 1 unless an individual had a very high white blood cell count—then we would have to cyto reduce.

One thing we were worried about was CNS [central nervous system] relapses, because we were moving away from chemotherapy. Most patients were older with a median age of 62 years. We have as of [the filming] 38 patients treated. The responses are great and CR is universal. CMR in the frontline setting is 85%, 60% after 1 month of therapy, and we’ve seen PCR [polymerase chain reaction] negativity after 1 week of therapy, which is surprisingly good.

For patients in the frontline cohort, no patient received transplant—none. They responded, maintained the response, and those who did not have a CMR, they are very close and remain on therapy.

From a safety point of view, we had no major safety concerns. Nobody had to stop ponatinib because of adverse events. We had 1 patient discontinue blinatumomab, an older patient, because of neurotoxicity—a recurring tremor—and we had 1 unrelated death from bleeding. The follow-up is still short, 12 months, but the estimated 3-year survival is 93%, same for relapse-free survival.

We have not done the extensive work for biology to look for the IKZF1 deletion and others, but so far with individuals responding it’s hard to identify a biomarker here. We’re looking as well at the kinetic of the T cells to see whether ponatinib plus blinatumomab can have some inhibition of the T cells. That remains to be defined. One thing we’re interested in looking at is the dynamic of the response, like in CML [chronic myelogenous leukemia]. Those who can have CMR after 1 or 2 weeks, will they be candidates for maybe discontinuation of therapy after 5 years? Today we give TKI for a lifetime, especially if transplant is not done. So maybe with such an early response, like that observed in CML, we will be able one day to treat these patients without chemotherapy, without transplant, and be able to cure them.

CORTES These are outstanding results, and it is amazing that we can do it without chemotherapy. The GIMEMA investigators were pioneers in doing these less intensive regimens and there was some debate there between the 2 strategies. Now we have this strategy that falls somewhere in between. Professor Foà, how do you see the 3 strategies playing together? How do you see them moving forward?

FOÀ For me it’s extremely rewarding.... We started using a TKI alone and steroids over 15 years ago in induction, and the first study was done in the elderly over 60 years up to 89 years, because it was ethically acceptable.

To see these data, for me it’s very rewarding because this goes in the line of what we’ve been doing for years. The incidence of the Ph-chromosome mutations increases with age; we’re talking about many patients over the age of 50 or 60 years, and they can be 70 or 80 years, where heavy chemotherapy is not easy, and a transplant even less so. This is an enormous opportunity we’re given.

I tell the students and fellows that in my day Ph-positive ALL was the worst leukemia you could get and possibly the worst cancer, because the only option was a transplant. But to get a transplant a patient had to respond to some form of treatment first, so it was a lethal disease. There’s a major change, to an extent that when you have a Ph-positive ALL in the ward you always are cheering that this is good news for the patient, which for me is a complete revolution.

**TABLE. Efficacy Results of Ponatinib and Blinatumomab in Phase 2 Study**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed Ph-positive ALL, relapsed or refractory Ph-positive ALL, or lymphoid accelerated or blast phase CML</td>
<td>Uncontrolled, active cardiovascular disease including congestive heart failure, uncontrolled hypertension Significant CNS pathology</td>
</tr>
<tr>
<td>Previous therapy with 1 to 2 courses of chemotherapy with or without TKI was allowed in the newly diagnosed cohort</td>
<td>Age ≥ 18 years</td>
</tr>
<tr>
<td>Age ≥ 18 years</td>
<td>ECGG status ≤ 2</td>
</tr>
<tr>
<td>Adequate hepatic function</td>
<td>Adequate renal function</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All patients (N = 35)</th>
<th>Frontline Ph-positive ALL (n = 20)</th>
<th>Relapsed or refractory ALL (n = 10)</th>
<th>CML-LBC (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRp (responders)</td>
<td>96%</td>
<td>100%</td>
<td>89%</td>
<td>100%</td>
</tr>
<tr>
<td>CMR</td>
<td>79%</td>
<td>85%</td>
<td>88%</td>
<td>40%</td>
</tr>
<tr>
<td>1-year OS rate</td>
<td>93%</td>
<td>93%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>2-year OS rate</td>
<td>80%</td>
<td>93%</td>
<td>53%</td>
<td>100%</td>
</tr>
<tr>
<td>1-year EFS rate</td>
<td>76%</td>
<td>93%</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>2-year EFS rate</td>
<td>70%</td>
<td>93%</td>
<td>41%</td>
<td>60%</td>
</tr>
</tbody>
</table>

CML-LBC, chronic myelogenous leukemia in lymphoblastic crisis; CMR, complete molecular remission; CR, complete response; CRp, complete responses with partial recovery of blood counts; EFS, event-free survival; OS, overall survival.
This should be a rise to the end of chemotherapy and induction. Will there be an end completely? That’s what I hope, and we hope to prove it—that, at least for a substantial fraction of patients, they will be treated without having chemotherapy and without a transplant, which I see as a major step forward. Not for all, and biology will tell us which, but I think for a high proportion, and that is a major step forward.

I love it, and I think that this is really practice changing. I’m excited as the MD Anderson team presents more data and longer follow-up. Obviously in Ph-positive ALL it’s a paradigm shift because we all worked hard to get these individuals to transplant early once they responded, and now we have other options. This is a real paradigm-shifting study.

Dr Jabbour, is hyper-CVAD-TKI dead?

Hyper-CVAD-TKI is dead. One observation I have from the trial is that when we started doing more FISH [fluorescence in situ hybridization] analysis, because prior you would get a diagnosis of Ph-positive ALL and that’s it. But now with further testing, we’re seeing, for example, FISH positivity in neutrophils or some myeloblasts and I do not know if it’s ALL Ph-positive disease or some disease evolving from CML background that all of us link to Ph-positive ALL.

We did see in a CML lymphoblast crisis de novo, those with p210 mutations, they did not do as well with the blinatumomab/ponatinib. [If they have a p210 mutation], I think they have CML in the background. And for those patients we said, “Well, maybe we still need to give the hyper-CVAD,” because with the hyper-CVAD plus ponatinib they did extremely well. There was no concern about CML lymphoblast crisis. We are being very careful right now to see whether blinatumomab/ponatinib will be appropriate for everybody, or maybe a subset of patients with CML evolving into ALL who will benefit from the hyper-CVAD strategy. They are all patients with ALL, but we need to keep watching carefully for them.

And then finally, those patients with an IKZF1 deletion where transplant is needed, I don’t think the hyper-CVAD will make a change. But we need more than blinatumomab/ponatinib for them.

I’ve been an advocate of trying to remove chemotherapy, apart from CNS prophylaxis. However, I think there are some categories of patients for whom we’ll have to continue chemotherapy, [in particular for those] who don’t obtain a CMR.

This then proposes the question, how do you define CMR? Is a PCR test good enough, or should we base this on NGS [next-generation sequencing] or digital droplet PCR, which is what we’re doing now? If a patient doesn’t become consistently negative molecularly, then I think we must add something more, and this presumably is chemotherapy or a direct transplant.

I think there are still some patients for whom let’s say systemic chemotherapy will still have a role. And the other group of patients, as alluded to already, is those who are IKZF1-positive who do significantly worse, at least with dasatinib (Sprycel)/blinatumomab. We’ll have to see how they perform with ponatinib/blinatumomab. We need the biology to guide us, so we need the assistance of the laboratories.

This is a key point at which to say the world is very vast, and in most parts of the world the biology is not available, so this is going to make it very difficult because if you have a patient who is MRD-positive, the patient is going to relapse, there’s no doubt about it. But if you don’t assess for MRD, you won’t know it. That is a key point that we should underline as much as possible, not only for those with Ph-positive disease but in general; we need accurate laboratories that work in the right way, because the MRD assessment must be done with the correct technology and in standardized laboratories.

—ROBIN FOÀ, MD

As Dr Jabbour mentioned earlier, with the response rate that they have and with the survival that they have, unless they didn’t have IKZF1 mutation, the combination seems to be pretty good across the board. Of course, it’s a small sample size. But I wanted to just throw in the question: With these results, what is the role of transplant today for patients with Ph-positive ALL?

My thinking is just sort of combining what people are saying, that you get an early signal of [individuals who] remain molecularly positive with a clear MRD. That may be a signal that it is time to shift gears from a low-intensity or a moderate-intensity therapy and maybe add chemotherapy. I do think transplant is still effective, and probably most effective in the MRD-negative state going into transplant. I would propose that for the MRD-positive, molecularly positive patient, the goal should be to switch gears, get them MRD-negative and try to transplant them at that point.

And I think that has probably the best chance to help a poor-risk patient do well long-term, at least until we can figure out whether there are other strategies to eliminate the idea of a transplant.

REFERENCES
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ALK Inhibitor Success Prompts Search for a Role Beyond NSCLC

by JANE DE LARTIGUE, PhD

THE RAPID DEVELOPMENT OF novel agents directed at anaplastic lymphoma kinase (ALK) gene fusions has emerged as one of the success stories of the targeted therapy era in non-small cell lung cancer (NSCLC). However, oncogenic activation of ALK, typically via fusions or other gene rearrangements, amplification, or activating point mutations (often accompanied by ALK protein expression), is seen in a range of other cancer types. This has prompted investigators to explore the question of whether ALK inhibitors can be effective in a broader landscape.

The first indication for ALK inhibitors outside of NSCLC has come in anaplastic large cell lymphoma (ALCL), where ALK gene fusions are found in up to 90% of pediatric cases. In January 2021, the FDA approved crizotinib (Xalkori) for the treatment of pediatric and young adult patients with ALK-positive ALCL, making it the first ALK inhibitor approved for this patient population in the United States. The second-generation ALK inhibitor alectinib (Alecensa) is approved in Japan for this indication.

Meanwhile, some neuroblastomas also are associated with activating ALK mutations, and crizotinib, alectinib, and the third-generation ALK inhibitor lorlatinib (Lorbrena) have demonstrated potential in this setting, with clinical trials ongoing.

Findings from case reports suggest ALK inhibitor activity occurs across a spectrum of other cancer types, but the low frequency of ALK-positive tumors can make searching for these patients similar to looking for a needle in a haystack, as some commentators have observed. Investigators are using novel trial designs to evaluate ALK inhibitors in a range of solid tumor types (TABLE), but for the time being, widespread clinical validation of ALK inhibitors beyond NSCLC remains elusive.

ALK IN DIVERSE TUMORS

ALK, a receptor tyrosine kinase, has been linked to cancer development since its identification in the 1990s. ALK was first described as the previously unknown gene juxtaposed with the nucleophosmin (NPM1) gene in a unique chromosomal rearrangement found in an ALCL cell line.

Subsequently, ALK gene fusions, predominantly the NPM1-ALK fusion, have been identified in nearly all pediatric and approximately half of adult cases of ALCL, a rare form of non-Hodgkin lymphoma.

Thanks to genome sequencing efforts, ALK gene fusions have been found across a wide range of cancer types, with multiple fusion partner genes. In lung cancer, the dominant ALK fusion is EML4-ALK, whereas approximately half of patients with inflammatory myofibroblastic tumors (IMFTs) display a TPM3/4-ALK fusion. Study results suggest that ALK fusions involving different partners vary in tumorigenic potential, but in each case the result is constitutive activation of ALK kinase. Other cancer types in which ALK fusions have been identified include renal, pancreatic, colorectal, breast, and thyroid cancers.

Neuroblastoma, a childhood cancer arising in immature nerve cells that accounts for approximately 10% of pediatric cancer deaths, is characterized by a different kind of oncogenic ALK alteration. Germline gain-of-function mutations in the ALK gene cause approximately half of all familial cases of neuroblastoma. ALK mutations also are observed in approximately 10% of patients with sporadic neuroblastoma.

These mutations are typically found within the kinase domain, driving ligand-independent ALK activation. In neuroblastoma, the most common germline ALK mutations are R1275Q, R1192P, and G1128A. R1275Q also is one of the most common sporadic mutations in ALK, in addition to F1174L and F1245C. The frequency of ALK mutations has been shown to increase in patients at relapse, as secondary mutations lead to the emergence of resistance.

In addition to fusions and mutations, ALK gene amplification and copy number gain are observed in many tumor types, including neuroblastoma, rhabdomyosarcoma, and esophageal cancer.

ALK-POSITIVE ALCL

ALK-positive ALCL has a better prognosis than ALK-negative disease and, in general, can be effectively treated in the front line with anthracycline-based chemotherapy. However, many patients experience disease relapse and have historically lacked effective treatment options.

The FDA approved crizotinib for the treatment of patients with relapsed/refractory ALK-positive ALCL based on data from the phase 1/2 ADVL0912 study (NCT00939770), in which ALK positivity was assessed by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) testing.

Investigators enrolled patients between 1 and 21 years of age with relapsed/refractory solid tumors or ALCL. During phase
**FOUND ON CHROMOSOME 2**, the ALK gene encodes a receptor tyrosine kinase in the insulin receptor superfamily. The ALK protein spans the plasma membrane, with an extracellular domain that binds to its activating ligand, triggering receptor dimerization, and an intracellular domain that contains its catalytic kinase domain, through which it facilitates the transfer of a phosphate group from adenosine triphosphate to key tyrosine residues within its dimer partner (trans-autophosphorylation) and then phosphorylates other target proteins.

Through target phosphorylation, ALK activates various downstream signaling cascades, including MAPK, PI3K/AKT, and JAK/STAT, through which it regulates numerous cellular processes, such as proliferation, survival, and differentiation, in response to extracellular stimuli (FIGURE). ALK is still considered an orphan receptor—i.e., one for which an endogenous ligand has not been identified. Several candidate ligands have been proposed, including midkine, pleiotrophin, heparin, FAM150A, and FAM150B, but the jury is still out on whether these represent true ligands that directly bind to and activate ALK.

**REFERENCES**

**FIGURE.** Activation of ALK Signaling

Under normal circumstances, ALK is activated through ligand binding with receptor phosphorylation (P) that then stimulates a cascade of downstream signaling, which can promote carcinogenic processes. Although ALK is still considered an orphan receptor, pleiotrophin (PTN) and midkine (MK) are secreted growth factors known to bind and activate signaling networks.

### TABLE. Ongoing Clinical Development of ALK Inhibitors in Non-NSCLC Tumors

<table>
<thead>
<tr>
<th>Drug (brand name; developer)</th>
<th>Patient population (trial name, if applicable; ClinicalTrials.gov identifier)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crizotinib</strong>&lt;sup&gt;a&lt;/sup&gt; (Xalkori; Pfizer)</td>
<td>Plus standard therapy in pediatric and young adult patients aged 1 to 30 years with high-risk neuroblastoma or ganglioneuroblastoma (NCT03126916)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pediatric and adult patients 6 years and older with neurofibromatosis type 2 and progressive vestibular schwannomas (NF1; NCT04283659)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Plus chemotherapy in pediatric patients under 18 years with relapsed/refractory solid tumors and AML (NCT02638428)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ALK fusion or mutation-positive advanced or metastatic solid tumors, NHL, and multiple myeloma in adolescent and adult patients 12 years and older (TAPUR; NCT02693533)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Advanced or metastatic non-clear cell RCC (INDIGO; NCT04644432)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Alectinib</strong>&lt;sup&gt;b&lt;/sup&gt; (Alecensa; Genentech)</td>
<td>Locally advanced or metastatic ALK-positive solid tumors as tested by NGS, excluding lung cancer and cancer of primary origin and excluding point mutations in ALK I1171X, G1202R, V1180L (Alpha-T-NCT04644315)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Advanced or metastatic non-clear cell RCC (INDIGO; NCT04644432)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Advanced or metastatic ALK-positive solid tumors excluding NSCLC (TAPISTRY; NCT04589845)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pediatric relapsed/refractory ALK fusion–positive solid or CNS tumors in patients up to 17 years (NCT04774718)</td>
<td>1/2</td>
</tr>
<tr>
<td></td>
<td>Plus RT in newly diagnosed GBM (NCT Neuro Master Match; NCT03158389)</td>
<td>1/2</td>
</tr>
<tr>
<td><strong>Lorlatinib</strong>&lt;sup&gt;b&lt;/sup&gt; (Lorbrena; Pfizer)</td>
<td>Relapsed/refractory ALK-rearranged ALCL (CRU3; NCT03505554)</td>
<td>2</td>
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<tr>
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<td>Monotherapy or with chemotherapy in pediatric and adult patients aged 1 to 90 years with relapsed/refractory neuroblastoma with activating ALK mutation, amplification, or fusion (NANT 2015-02; NCT03107988)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Ceritinib</strong>&lt;sup&gt;b&lt;/sup&gt; (Zykadia; Novartis)</td>
<td>Advanced/metastatic soft tissue sarcoma (MULTISARC; NCT03784014)</td>
<td>3</td>
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<td></td>
<td>Plus standard therapy in pediatric and young adult patients up to 22 years with newly diagnosed high-risk neuroblastoma (PEDS-PLAN; NCT02559778)</td>
<td>2</td>
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<td>Plus ribociclib (CDK4/6 inhibitor) in pediatric and young adult patients aged 1 to 21 years with relapsed/refractory ALK mutation–positive neuroblastoma (NEPENTHE; NCT02780128)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Brigatinib</strong>&lt;sup&gt;b&lt;/sup&gt; (Alunbrig; Takeda)</td>
<td>Multiple tumor types associated with neurofibromatosis type 2 in adolescent and adult patients 12 years and older (INTUITT-NF; NCT04374305)</td>
<td>2</td>
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<td>Pediatric and young adult patients aged 1 to 25 years with ALK protein–positive ALCL, as well as ALK fusion or mutation–IMFT and other solid tumors (Briga-PED; NCT04925609)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><strong>Entrectinib</strong>&lt;sup&gt;b&lt;/sup&gt; (Rozitriek; Genentech)</td>
<td>Advanced/metastatic solid tumors with ALK fusions or rearrangements (STARTTRK-2; NCT02568267)</td>
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<td>Advanced/metastatic solid or primary CNS tumors with ALK molecular alterations (fusion or nonfusion) in pediatric patients aged up to 18 years (STARTTRK-NG; NCT02650401)</td>
<td>1/2</td>
</tr>
<tr>
<td><strong>Ensartinib</strong> (X-396; Xcovery)</td>
<td>Melanoma with ALK alterations (NCT03420508)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Pediatric and young adult patients aged 1 to 21 years with relapsed/refractory advanced solid tumors, NHL, or histiocytic disorders with ALK fusions or missense mutations (A Pediatric MATCH Treatment Trial; NCT03213652)</td>
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<tr>
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<td>Pediatric and young adult patients aged 1 to 21 years with relapsed/refractory advanced solid tumors, NHL, or histiocytic disorders with ALK gene alterations (The Pediatric MATCH Screening Trial; NCT03155620)</td>
<td>2</td>
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* Trial is not yet recruiting.

* Trial is active but not recruiting.

1 dose escalation, twice-daily doses up to 280 mg/m2 were well tolerated. Several phase 2 dose-expansion cohorts were undertaken, including in patients with ALK-positive ALCL who previously received at least 1 systemic therapy. These patients received twice-daily crizotinib at 280 mg/m2 (n = 20) or 165 mg/m2 (n = 6).17,14 An objective response rate (ORR) of 88% (95% CI, 71%-96%) was observed, which included complete responses (CRs) in 81% of patients. Responses continued for 6 months in 39% of patients and for 12 months in 22%.

All patients treated at the dose of 280 mg/m2 experienced at least 1 grade 3 or higher adverse event (AE), which was considered possibly, probably, or definitely linked to crizotinib in 85% of cases, most commonly neutropenia.17,18

Alectinib was evaluated in a clinical trial involving relapsed/refractory ALK-positive ALCL in Japan. In February 2020, Chugai Pharmaceutical, the Japanese subsidiary of Roche, announced the approval of alectinib for this indication based on the demonstration of an ORR of 80% (90% CI, 56.2%-95.9%), including 6 CRs and 2 partial responses (PRs), among 10 patients enrolled in the phase 2 trial (UMIN-CTR unique trial No. UMIN000016991). One-year progression-free (PFS), event-free survival, and overall survival (OS) rates were 58.3% (90% CI, 28.6-79.3%), 70.0% (90% CI, 39.6-87.2%), and 70.0% (90% CI, 39.6-87.2%), respectively. The most common AEs were diarrhea, upper respiratory infection, rash, and increased levels of alkaline phosphatase, whereas neutropenia was the most common AE of grade 3 and above.8

**BROADER CLINICAL VALIDATION**

In February 2021, investigators from the Children’s Oncology Group published results from the neuroblastoma cohort of the ADV10912 trial. Among 20 patients with neuroblastoma who received twice-daily crizotinib at 280 mg/m2, the ORR was 15% (95% CI, 3.3%-34.3%), including 1 CR and 2 PRs. All responding patients displayed the R1275Q mutation.11 Lorlatinib is being studied in the phase 1 NANT 2015-02 trial (NCT03107988) in patients with ALK-positive neuroblastoma. Preliminary results were recently published.18
reported; 32 patients with relapsed/refractory neuroblastoma with ALK mutations or amplification were treated at doses of 45, 60, 75, 95, or 115 mg/m²/day for patients 18 years and younger (pediatric cohort; n = 21) and at 100 or 150 mg/m²/day for patients older than 18 years (adult cohort; n = 11).13

The pediatric cohort had 1 CR, 1 PR, 3 minor responses, and 5 patients with stable disease (SD); in the adult cohort, there were 2 CRs, 3 PRs, 3 minor responses, and 2 cases of SD. The most common treatment-related AEs included weight gain, hypertriglyceridemia, and high cholesterol. Memory and concentration impairment of grade 1/2 severity were the most common neurocognitive toxicities in the adult cohort.13

The ADVL0912 trial also included 14 patients with ALK-positive IMFT. In this population, crizotinib was also found to be highly effective, with an ORR of 86% (95% CI, 57%-98%), including CRs in 36% of patients.18 The CREATE study (NCT01524926) enrolled multiple cohorts of patients with MET- or ALK-driven cancers to be treated with crizotinib. In a cohort of patients with ALK-positive IMFT (n = 12), the ORR was 50% (95% CI, 21.1%-78.9%). The disease control rate was 100% (95% CI, 73.5%-100%), and 1-year PFS and OS rates were 73.3% (95% CI, 37.9%-90.6%) and 81.8% (95% CI, 44.7%-95.1%), respectively. Common AEs included nausea, fatigue, blurred vision, vomiting, and diarrhea.20

In the phase 1b PROFILE 1013 trial (NCT01121588), crizotinib was studied in non-NSCLC tumors in which ALK gene translocation or inversion events were determined by IHC, FISH, or reverse transcriptase polymerase chain reaction or sequencing. Investigators observed objective responses in 53% of patients with lymphoma, including 8 CRs and 1 PR, and in 67% of patients with IMFT, including 1 CR and 5 PRs.21

PROFILE 1013 also enrolled 17 patients with a variety of other ALK-positive tumor types. Among these patients, the ORR was 12% and included 2 PRs in patients with colorectal and medullary thyroid cancer.21

Beyond this, evidence of the activity of other next-generation ALK inhibitors is limited largely to case reports for ceritinib (Zykadia) and preclinical activity for brigatinib (Alunbrig), although numerous clinical trials are ongoing, according to a search of ClinicalTrials.gov.

These case reports suggest potential activity of ALK inhibitors across a spectrum of ALK-positive cancers, including renal, breast, ovarian, prostate, and colorectal cancers,3,22,23 Notably, a recent study identified 7 patients with rare ALK-positive tumors who had been treated outside of clinical trials with either alectinib (n = 5) or crizotinib (n = 2) as initial therapy. The ORR for the initial therapy was 85.7% (95% CI, 44%-97%). There were 2 CRs and 2 PRs among the 5 patients receiving alectinib, and both of those receiving crizotinib experienced PRs. Tumor types included IMFT, histiocytosis, histiocytic sarcoma, osteosarcoma, and parotid adenocarcinoma.24

Because of the low frequency of ALK alterations and heterogeneity in the specific types of ALK alterations involved, investigators have found that conducting randomized clinical trials of ALK inhibitors in non-NSCLC tumors is extremely challenging. They have turned to basket and umbrella trial designs that enroll patients with ALK alterations irrespective of histology.1

Two such trial designs were highlighted at the 2021 American Society of Clinical Oncology Annual Meeting. In the phase 2 TAPSTRY trial (NCT04589845), patients with ALK fusion-positive non-NSCLC tumors are being enrolled to an alectinib treatment arm.25 The phase 2 ALpha-T trial (NCT04644315) is administering alectinib to adults with any locally advanced or metastatic solid tumor, excluding lung cancer and cancer of unknown primary, that harbors an ALK fusion or selected mutation (R1275Q, F1245C, F1174X). This trial is testing a novel decentralized design that permits enrollment regardless of location and allows most assessments to be performed at home by a mobile nurse.26

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ACQUIRED RESISTANCE TO endocrine therapy has presented challenges for patients with hormone receptor-positive breast cancer. Historically, improvements in both survival and quality-of-life outcomes have made endocrine therapy the backbone of treatment for this patient population. However, up to 40% of tumors initially responsive to endocrine therapy develop resistance to the treatment. Investigators have turned their attention to identifying tactics to circumvent mechanisms of resistance. Two of the most prominent avenues have been the investigations of combination therapies leveraging CDK4/6 inhibitors and PI3K inhibitors.

During a recent OncLive Peer Exchange, a panel of breast cancer experts discussed the latest data for CDK4/6 inhibitors and PI3K inhibitors in patients with hormone receptor-positive advanced breast cancer, and they shared their experience using these agents in their practices. “We need to hit the cancer hard where it hurts and not allow for the disease burden to increase, the number of cells to increase, or the number of resistance mechanisms to increase,” Dejan Juric, MD, said.

CDK4/6 INHIBITORS: LATEST OS DATA
Three CDK4/6 inhibitors have been approved by the FDA for patients with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer (TABLE). Initial approvals were based on improvements in progression-free survival (PFS). However, data from multiple clinical trials have since shown an overall survival (OS) benefit with these agents.

In the second- and subsequent-line settings, the MONARCH-2 trial (NCT02107703) showed a clinically meaningful median OS benefit of 9.4 months with the addition of abemaciclib (Verzenio) to fulvestrant in women with hormone receptor-positive, HER2-negative advanced breast cancer that had progressed on endocrine therapy, regardless of their menopausal status. In the PALOMA-3 trial (NCT01942135), after a median follow-up of 44.8 months, the addition of palbociclib (Ibrance) to fulvestrant led to a 6.9-month OS benefit in patients with hormone receptor-positive, HER2-negative advanced breast cancer that had previously responded to endocrine therapy. Specifically, the reported median OS was 34.9 months in the palbociclib arm vs 28.0 months in the placebo arm (P < .0221). Furthermore, after a median follow-up of 73.3 months, this benefit was maintained with a median OS of 34.8 months in the palbociclib arm and 28.0 months in the placebo arm (P < .0221). “[PALOMA-3] is a unique trial in that it included patients who had received about a third of prior chemotherapy and multiple lines of treatment, and the control arm didn’t do as well,” said Hope S. Rugo, MD, FASCO.
a 2020 Giants of Cancer Care award winner in the education category. “This suggests that the group who didn’t get chemotherapy, who presumably are more sensitive to endocrine therapy overall, had a survival difference in line with the other trials.”

Similarly, an OS benefit has also been observed with ribociclib (Kisqali). In the MONALEESA-3 trial (NCT02422615), which included postmenopausal women treated in both the first- and second-line settings with ribociclib plus fulvestrant or placebo plus fulvestrant, treatment benefit was seen in both ribociclib-treated populations. “[Investigators have] showed that in the second-line setting, the absolute difference in OS is highly significant, and there’s a 6-month difference. They still haven’t reached the median in the first-line setting, but the hazard ratio is 0.64, showing a benefit in the first-line setting in this group of postmenopausal patients,” Rugo said.

MONALEESA-7 (NCT02278120) was the first clinical trial to show a statistically significant OS benefit with a CDK4/6 inhibitor plus endocrine therapy in the first-line setting for patients with advanced breast cancer, Rugo said. The trial randomly assigned pre- or perimenopausal patients with hormone receptor-positive, HER2-negative advanced breast cancer 1:1 to receive ribociclib or placebo plus goserelin with either a nonsteroidal aromatase inhibitor (ie, letrozole or anastrozole) or tamoxifen.3 After a median follow-up of 53.5 months (minimum, 46.9 months), the median OS was 58.7 months with ribociclib plus endocrine therapy vs 48.0 months with placebo plus endocrine therapy (HR, 0.76; 95% CI, 0.61-0.96). A similar survival benefit was observed with ribociclib in the patients who received a nonsteroidal aromatase inhibitor, with a median OS of 58.7 months vs 47.7 months (HR, 0.80; 95% CI, 0.62-1.04). “The median OS was increased by [approximately] 11 months...this [trial included] almost 700 patients, and the data [were] practice-changing,” Rugo said.

Based on the data from these clinical trials and other trials that have shown significant benefit across end points—including time to first chemotherapy, chemotherapy-free survival, and PFS—the panelists noted that it is difficult to find a patient with hormone receptor-positive, HER2-negative breast cancer who should not receive a CDK4/6 inhibitor, especially in the first-line setting. “Later use of these therapies can be problematic,” Juric said. “Some patients may never get that treatment if something catastrophic happens in the first-line setting.” He explained that although these patients historically had an OS of approximately 2 years, data from newer studies that added CDK4/6 inhibitors have reported median OS of 4 or 5 years, making them an invaluable treatment option.

Juric said he pays particular attention to the population in which the primary data were generated. “If I have a premenopausal patient, I’m prescribing ribociclib. If I have a patient who has primary endocrine-resistant breast cancer, a high visceral disease burden where ER and [progesterone receptor] status are questioned in terms of their amount or positivity, and I’m not worried about [gastrointestinal] toxicity, then I really like abemaciclib,” he said.

Although these agents are similar and are all classified as CDK4/6 inhibitors, Juric said they are different drugs with different chemical structures and different target inhibition profiles. “Breast cancers tend to be really dependent primarily on CDK4, at least initially, and palbociclib is equipotent there, whereas the other 2 drugs preferentially hit CDK4. That may not necessarily come into play initially in the first readouts of these trials, but they may play a role as you start looking at a longer effect or more distant clinical end points,” he said.

### SELECTING BETWEEN CDK4/6 INHIBITORS

Investigators have not produced comparative data between palbociclib, ribociclib, and abemaciclib.

**Moderator Andrew D. Seidman, MD**, asked the panelists how they “parse this embarrassment of riches” to decide which agent to use for their patients. The panelists cited a variety of factors when deciding, such as differences in eligibility criteria between clinical trials, toxicity profiles, drug targets, access and finance issues, and ease of dose reduction.

### Table. Overview of CDK4/6 Inhibitors for Patients With Hormone Receptor–Positive, HER2-Negative Advanced or Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial US approval</th>
<th>Formulations and recommended administration</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (Ibrance) 2015</td>
<td>Capsules or tablets: 125 mg, 100 mg, 75 mg</td>
<td>With an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women, or in men</td>
<td></td>
</tr>
<tr>
<td>Ribociclib (Kisqali) 2017</td>
<td>Tablets: 200 mg</td>
<td>With an aromatase inhibitor as initial endocrine-based therapy in pre/perimenopausal or postmenopausal women</td>
<td></td>
</tr>
<tr>
<td>Abemaciclib (Verzenio) 2017</td>
<td>Tablets: 50 mg, 100 mg, 150 mg, 200 mg</td>
<td>With an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women</td>
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</table>

**Note:**
- **Palbociclib (Ibrance)** is approved for use as monotherapy for adult patients with disease progression following endocrine therapy.
- **Abemaciclib (Verzenio)** is approved for use as monotherapy for adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
of OS for palbociclib compared with real-world evidence. "Subsequent analysis has been conducted, as well as exploratory and other interesting OS analyses of palbociclib examined real-world evidence for instance, those from the Flatiron database," McAndrew said. "These data suggest that there is potentially OS benefit with palbociclib and it makes one more inclined to really question whether these differences in survival that we are seeing [are]

primarily because of study design and inclusion of patients who just weren’t included in the other trials."

Aditya Bardia, MD, MPH, discussed the toxicity profiles of the agents and ease of dosing, noting "ribociclib and palbociclib tend to cause more myelosuppression, and abemaciclib tends to cause more diarrhea." He explained that when dose reduction becomes necessary with these agents, it is more challenging with palbociclib because "you must change pills from 125 mg to 100 mg, whereas with ribociclib, you start with 3 tablets and then reduce to 2 tablets." Subsequently, palbociclib requires "another call to the insurance company and getting the new supply of 100 pills," he said.

CONSIDERING PIK3Ca MUTATIONS

Activating mutations in PIK3Ca and resultant activation of the protein can be found in approximately 40% of patients with ER-positive metastatic breast cancer, Juric said, emphasizing that PIK3Ca should be looked for upon obtaining the first diagnostic specimen. "PIK3Ca is an important regulator of cell signaling, mediating growth signals that come from the membrane of the cell and go into the cell cycle machinery," he added.

Although activation of the PI3K pathway via PIK3Ca mutations is associated with poor prognosis in patients with hormone receptor-positive, HER2-negative advanced breast cancers, the SOLAR-1 trial (NCT02437318) showed a 7.9-month numeric improvement in median OS in these patients when the PI3K inhibitor alpelisib (Piqray) was added to fulvestrant. In the PIK3Ca-mutant cohort, the median OS was 39.3 months (95% CI, 34.1-44.9) in the alpelisib arm vs 31.4 months (95% CI, 26.8-41.3) in patients treated with placebo plus fulvestrant. However, the OS results did not cross the prespecified efficacy boundary. In patients with lung and/or liver metastases, the median OS was 37.2 months (95% CI, 28.7-43.6) with alpelisib vs 22.8 months (95% CI, 19.0-26.8) with placebo (HR, 0.68; 95% CI, 0.46-1.00). "When we looked at the visceral group of patients, [a group] that we would have expected to do more poorly, we saw a suggestion of a benefit," Rugo said. "Even though you can’t make a statistical conclusion about that, it’s very encouraging for us in treating patients in this setting where you want to avoid going to chemotherapy."

Because patients with PIK3Ca mutations are known to have poorer outcomes, Juric emphasized the importance of using drugs such as alpelisib for these patients in the clinical setting or seeking out clinical trials. "[SOLAR-1 data match] some of the other analysis of CDK4/6 clinical trials, including MONARCH-2 and MONALEESA-3 trials," he said. "Results of the studies of abemaciclib and the ribociclib in ER-positive disease have shown that patients with PIK3CA mutations tend to perform less well in both the CDK4/6 arm and the control arm." Juric noted that although PIK3Ca is not necessarily a predictor of CDK4/6 benefit, "if you look at absolute numbers, [these patients] tend to perform less well compared with wild types in both arms," making it important to consider additional treatment strategies for these patients, such as PI3K inhibitors.

The SOLAR-1 trial focused on 11 mutations involving exon 7, 9, and 20 of the PIK3Ca gene, most of which were hotspot mutations, according to Juric. He said that these mutations make up approximately 80% of all PIK3Ca mutations and the benefit of adding alpelisib to fulvestrant is "undeniable" for these patients. An area in which further study is needed is for patients with nonhotspot mutations that can also activate the protein, he said. "With nonhotspot mutations we have to work with our microbiologist....I’ll give you an example: R88Q was not in the initial 11 mutations of SOLAR-1. But is that mutation altering the function of the protein? Is it likely to activate the pathway? If it is, I would argue that this is the setting [in which] we should be studying or using PI3Ka inhibitors such as alpelisib," he said.

The panelists proceeded to discuss real-world data supporting the use of the PIK3Ca inhibitor alpelisib in combination with fulvestrant for patients with PIK3Ca-mutant, hormone receptor-positive, HER2-negative advanced breast cancer, including a study that assessed data from 10 centers throughout France. In total, 209 patients who had previously received at least 2 prior systemic treatments (median, 4), including an aromatase inhibitor and a CDK4/6 inhibitor, were treated provided they did not have any contraindications. The investigators found the combination of alpelisib and fulvestrant to have clinically relevant efficacy and to be well tolerated, with the most common grade 3/4 adverse effects being hyperglycemia, skin rash, diarrhea, and fatigue. The investigators also assessed for predictors of response to the combination. “They found that prior use of everolimus [Afinitor] was not a predictive factor in terms of doing worse or better with alpelisib,” Bardia said. “Surprisingly, prior use of fulvestrant was associated with improved outcomes with fulvestrant plus alpelisib.”

When it comes to assessing patients for PIK3Ca mutations, Bardia said his institution performs genotyping of tissue specimens when available, particularly in the first-line setting. Thereafter, they usually perform plasma-based genotyping. “An advantage of plasma-based genotyping is that if the initial tissue-based genotyping shows a PI3K mutation and the patient has progression on letrozole plus a CDK4/6 inhibitor, a subset could have acquired PIK3Ca mutations that you can detect in the blood,” he said. “To give the patient the maximum chance of getting access to a PI3K inhibitor, that’s a really good time to get plasma-based genotyping.”

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

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