Surge of New Drugs Fuels Optimism in Pediatric Oncology

PEER EXCHANGE
10 Combos Dominate Frontline RCC Choices

Concurrent Mutations Are Targeted in NSCLC

CLINICAL PERSPECTIVES
Debu Tripathy, MD, on Tackling ESR1 Mutations in BREAST CANCER
Robert L. Coleman, MD, on Novel CERVICAL CANCER Therapies
Scott Kopetz, MD, PhD, on Vemurafenib CRC Triplet

UAMS WINTHROP P. ROCKEFELLER CANCER INSTITUTE
Monoclonal Antibodies Prove to Be Novel Therapeutics for MYELOMA
BY FRITS VAN RHEE, MD, PhD
ARE YOU THINKING DEEP ENOUGH
IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA?

Relapse is expected, but deep response could be too¹²

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

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

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

Visit ThinkDeepMM.com

OS=overall survival, PFS=progression-free survival

<table>
<thead>
<tr>
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<tbody>
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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 72.
Named one of the 10 best hospitals for Cancer in the U.S.

At Cedars-Sinai, the dedication of our doctors and staff has made us one of the most recognized hospitals in the nation. We’re proud to have earned a place on U.S. News & World Report’s Best Hospitals Honor Roll. This recognition belongs to our entire team who shows up day after day, night after night, for all of Southern California.

Learn more about our cancer care: cedars-sinai.org/cancer
Surge of New Drugs Fuels Optimism in Pediatric Oncology

by MEIR RINDE

The FDA approved 8 new drugs or indications for pediatric patients with cancer in 2020, significantly expanding the treatment options for subsets of children and adolescent/young adults. Experts in the field attribute the advancements to an improved understanding of disease biology, more inclusive clinical trial strategies, and regulatory initiatives.

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By Maurie Markman, MD

Medical World News®

FDA Digest

Pipeline Report:
New Drugs of 2020

Drug Spotlight:
Relugolix (Orgovyx)
CONTENTS

70  Biden Issues Health Care Executive Orders
By Keith A. Reynolds

FEATURES

Partner Perspectives

72  Monoclonal Antibodies Prove to Be Novel Therapeutics for Myeloma
By Frits van Rhee, MD, PhD

OncPathways®

74  Bad Company: Concurrent Mutations Define Unique Subsets of NSCLC
By Jane de Lartigue, PhD

OncLive Peer Exchange®

78  Immuno-Oncology Combinations Dominate in Frontline Treatment of Advanced Clear Cell RCC
By Christina T. Loguidice

Chairman’s Letter

Precision Medicine Hits New Milestones

SINCE THE INTRODUCTION OF targeted therapies into the cancer treatment landscape more than 20 years ago, there has been much debate about the potential benefits of precision medicine and how best to harness technology to improve outcomes. At times, the debate has revolved around the hope versus the hype for molecularly targeted strategies.

Now we are seeing the benefits of precision medicine on many fronts and, when it comes to pediatric cancer, the promise of this approach is hardly an overstatement. At the end of 2019, there were just 46 treatment and supportive care products with specific indications for children with cancer. In 2020 alone, the FDA approved 8 new drugs or indications—an increase of approximately 17%,1,2

This expansion of available therapeutics did not come about by some happenstance of drug development. Instead, a series of federal legislative actions starting in 1997 improved pharmaceutical industry incentives in this space. At the same time, investigators have honed the design of clinical trials evaluating molecular targets and the art of including children and adolescents in adult studies. Experts describe the interplay of these trends in delivering advancements in pediatric oncology in the cover story of this issue of OncologyLive®.

The broad application of next-generation sequencing is poised to enhance outcomes further. As research moves forward, molecular analyses are growing increasingly granular. In non–small cell lung cancer, for example, we have become accustomed to hearing about the impact of KRAS mutations. Part of the research focus, as we report in the OncPathways® article in this issue, involves identifying other genes concurrently mutated with KRAS and the potential for targeting co-occurring alterations as a therapeutic strategy.

These developments are exciting and gratifying. As we enter the 2021 conference season, our editorial team is seeking out the latest and most impactful data that will help inform clinical practice. Please check out our coverage at OncLive.com.

As always, thank you for reading.
Mike Hennessy Sr
Chairman and Founder

REFERENCES
For adults with intermediate- or high-risk myelofibrosis (MF)¹

**INTERVENE**

WITH

**JAKAFI® (RUXOLITINIB)**

**AT DIAGNOSIS**

---

**Ruxolitinib (Jakafi)** is a Category 2A* treatment option for both symptomatic lower-risk¹ and higher-risk MF – in patients with platelets ≥50 x 10⁹/L.²

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.²

¹Lower-risk MF is defined as low or intermediate-1 risk based on DIPSS, DIPSS-Plus, and MYSEC-PM, low or intermediate risk based on MIPSS-70 (threshold of ≤3 prognostic variable points), and very low, low, or intermediate risk based on MIPSS-70+ (version 2.0; threshold of ≤3 prognostic variable points).²

²In patients who are not transplant candidates.

---

**SIGNIFICANTLY MORE PATIENTS RECEIVING JAKAFI EXPERIENCED IMPROVEMENT IN MF-RELATED SPLENOMEGALY¹,³,⁵**

**COMFORT-I PRIMARY ENDPOINT¹,³,⁵**

<table>
<thead>
<tr>
<th>42% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 24</th>
<th>VS</th>
<th>0.7% of patients receiving placebo (P &lt; 0.0001)</th>
</tr>
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</table>

4.4 years median duration of spleen response among primary responders (n = 65)⁴

**COMFORT-II PRIMARY ENDPOINT¹,⁵,₁¹**

<table>
<thead>
<tr>
<th>29% of patients receiving Jakafi achieved a ≥35% reduction in spleen volume at week 48</th>
<th>VS</th>
<th>0% of patients receiving best available therapy¹ (P &lt; 0.0001)</th>
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</thead>
</table>

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**Indications and Usage**

Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocytopenia MF in adults.

**Important Safety Information**

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC < 0.5 x 10⁹/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi. When PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt
JAKAFI 3-YEAR AND 5-YEAR OVERALL SURVIVAL ANALYSES

**COMFORT-I: 5-YEAR ANALYSIS OF JAKAFI AND PLACEBO**
- At 3 years, survival probability was 70% for patients originally randomized to JAKAFI and 61% for those originally randomized to placebo.
- Overall survival was a prespecified secondary endpoint in COMFORT-I.

**JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 51%**
- All patients in the placebo group either crossed over to JAKAFI at a median of 9 months or discontinued.

**COMFORT-II: 5-YEAR ANALYSIS OF JAKAFI AND BEST AVAILABLE THERAPY**
- At 3 years, survival probability was 79% for patients originally randomized to JAKAFI and 59% for those originally randomized to best available therapy.
- Overall survival was a prespecified secondary endpoint in COMFORT-II.

**JAKAFI 5-YEAR OVERALL SURVIVAL PROBABILITY WAS 56%**
- All patients in the best available therapy group either crossed over to JAKAFI at a median of 17 months or discontinued.

For more data on long-term outcomes with JAKAFI, visit JakafiResults.com.

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

To learn more about JAKAFI, visit HCP.Jakafi.com.

**Oral Jakafi (ruxolitinib) tablets**
- Indications and Usage: Treatment with JAKAFI can cause thrombocytopenia, anemia weeks until doses are stabilized, and then as clinically indicated. Use active surveillance and prophylactic antibiotics according to withholding or interrupting JAKAFI for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation.
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations.
- Treatment with JAKAFI has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, triglycerides. Assess lipid parameters 8-12 weeks after initiating JAKAFI. Monitor and treat according to clinical guidelines for hyperlipidemia.
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥50%) were infections.
- Dose modifications may be required when administering JAKAFI with strong CYP3A4 inhibitors or fluorocoumaline or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy.
- Use of JAKAFI during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking JAKAFI should not breastfeed during treatment and for 2 weeks after the final dose.

Infection Information

Infections taking Jakafi. The effect of Jakafi on viral replication in Herpes Zoster residence in or travel to countries with a high prevalence of active serious infections have resolved. Observe patients receiving to continue Jakafi during treatment of active tuberculosis should primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.

CONTRAINDICATIONS

Chronic HBV infection should be treated and monitored according to the overall risk-benefit determination.

ADMINISTRATION (2), and Adverse Reactions (6.1) in Full Prescribing Information. Jakafi. Platelet transfusions may be necessary [see Warnings and Precautions (5.1) in Full Prescribing Information] • Risk of infection [see Warnings and Precautions (5.4) in Full Prescribing Information].

Clinical Trials Experience in Myelofibrosis Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 × 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 × 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the platelet count during the first 6 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse reactions were thrombocytopenia and anemia [see Table 2]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [see Table 4]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common hematologic adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment. The incidence of Grade 2 and 3 adverse events was lower in patients treated with placebo than in patients treated with Jakafi. The most frequent hematologic adverse reactions occurring in patients who received Jakafi were thrombocytopenia (17%), neutropenia (17%), anemia (16%), and gastrointestinal events (14%).

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Thrombocytopenia</td>
<td>70</td>
<td>9</td>
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<tr>
<td>Anemia</td>
<td>96</td>
<td>11</td>
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<tr>
<td>Neutropenia</td>
<td>19</td>
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Table 3: Polycythemia Vera: Nonhematologic Adverse Reactions Occurring in ≥5% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Best Available Therapy (N=111)</th>
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<tr>
<td>Diarrhea</td>
<td>15</td>
<td>7</td>
<td>&lt;1</td>
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<tr>
<td>Dizziness</td>
<td>15</td>
<td>0</td>
<td>16</td>
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<tr>
<td>Fatigue</td>
<td>13</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Muscle Spasms</td>
<td>12</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Constipation</td>
<td>8</td>
<td>3</td>
<td>0</td>
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</tbody>
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Table 3 continued above.
Table 3 continued.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>72 &lt;1 -1 24 3</td>
<td>58 0 0</td>
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<tr>
<td>Thrombocytosis</td>
<td>27 5 3 1</td>
<td>24 3 1</td>
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<tr>
<td>Neutropenia</td>
<td>3 &lt;1 -1 0</td>
<td>10 0 0</td>
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<td>Chemistry</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>35 0 0 0</td>
<td>8 0 0</td>
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<tr>
<td>Elevated ALT</td>
<td>25 &lt;1 -1 0</td>
<td>16 0 0</td>
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<tr>
<td>Elevated AST</td>
<td>23 0 0 1</td>
<td>23 1 0</td>
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<tr>
<td>Hypertiglyceridemia</td>
<td>15 0 0 0</td>
<td>13 0 0</td>
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</table>

*Presented values are worst Grade values regardless of baseline

Table 5: Acute Graft-versus-Host Disease: Nonhematologic Adverse Reactions Occurring in ≥15% of Patients in the Open-label, Single-Cohort Study

<table>
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<tr>
<th>Adverse Reaction</th>
<th>Jakafi (N=71)</th>
<th>Worst Grade during treatment</th>
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<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 &lt;1 -1</td>
<td>4 3 0</td>
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<tr>
<td>Hypertension</td>
<td>20 13</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Trial Experience in Acute Graft-versus-Host Disease

In a single-arm, open-label study, 71 adults (ages 17-73 years) were treated with Jakafi for acute GvHD failing treatment with steroids with or without other immunosuppressive drugs [see Clinical Studies (14.3) in Full Prescribing Information]. The median duration of treatment with Jakafi was 46 days (range, 4-382 days). There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in termination of treatment occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 5 shows the adverse reactions other than laboratory abnormalities.

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Cancer Staging and Toxicity Framework Should Be Overhauled for the Modern Era

by MAURIE MARKMAN, MD

The management and outcomes for a large proportion of advanced cancers have changed rather substantially over the past 10 to 20 years. It was not that long ago, for example, when standard therapy for metastatic lung cancer was simply cytotoxic chemotherapy and the only relevant distinction in the agents used was the division between small cell and non–small cell lung cancer. Formerly, small cell lung cancer was generally considered more chemotherapy sensitive in the short term but also associated with an overall inferior survival outcome; however, the difference in prognosis compared with metastatic non–small cell lung cancer was measured in months—rarely longer.

Terms such as cure or even prolonged survival were rarely used when discussing the vast majority of advanced, metastatic, or recurrent solid tumors. In general, when employing cytotoxic chemotherapy during this era, the realistic goals of the therapeutic regimen were limited extension of overall survival, palliation of existing symptoms, or prolongation of the time to subsequent disease progression or development of symptoms. Of course, there were important exceptions to this distressing status quo, such as patients with advanced germ cell tumors (both male and female) and, occasionally, patients with epithelial ovarian cancer, who would achieve extended disease-free survival.

Further, antineoplastic therapies (excluding hormonal manipulations such as in cancers of the breast and prostate) were often quite brutal in their short-term effects, including substantial emesis and other effects on the gastrointestinal tract, fatigue, and bone marrow suppression. In addition, more long-term, potentially devastating toxicities, including cardiomyopathy and peripheral neuropathy, were not rare. It was not uncommon for patients to simply decline suggested treatments as the cancer worsened, in view of the toxicities they had already encountered or were likely to experience with additional drug delivery. Treating oncologists commonly heard statements such as “chemotherapy is worse than the cancer” and “life is not worth living if I take these drugs.”

In the early days of the modern oncology era, it was often appropriate to suggest that the only realistic chance for cure was surgical, with local radiation adding a relevant component to prevent local tumor spread and morbidity. If chemotherapy was indicated, the prognosis for solid tumors—with a few relevant exceptions—was dismal.

This was the state of affairs when 2 universally used standard definitions and terminologies were introduced and subsequently became foundational for the entire field of oncology: the cancer staging system and the toxicity scales routinely employed in clinical trials.

One can certainly understand the goals and utility of this framework in a clinical universe where solid tumors are either cured (or not) through surgical removal, and where the presence of metastatic disease discovered at initial diagnosis or at a subsequent point in time in the natural history of a cancer is characterized by short-term survival (measured in months, if not weeks). One can understand all this when antineoplastic therapy is delivered rather briefly in view of both its limited effectiveness and serious adverse effects, and where the realistic hope associated with the introduction of a new therapy would be to permit patients to extend their survival, albeit modestly.

Shortcomings of the current standards

The critical question now is whether the existing cancer staging system and the standard toxicity scales accurately...
reflect cancer management in 2021 and beyond and, to be blunt, whether the current system has outlived its usefulness.

First, let us consider cancer staging. This well-established and meticulously defined system is foundational in cancer management and is a core component in defining both prognosis and treatment. However, the fact that the formal process of staging is undertaken once, and only once, during the natural history of a patient’s cancer journey is increasingly problematic. Many cancers are being appropriately viewed as chronic conditions, where the patient’s ultimate survival even when surgical cure is not possible may be measured in years rather than months or weeks.

In fact, the current staging terminology is increasingly unhelpful and can be confusing to clinicians and patients alike. A given cancer may locally or regionally recur or metastasize after, for example, initially being staged as a localized mass (stage 1) with no lymph node involvement (eg, T2, N0, M0) but that cancer does not now become characterized as stage 4 due to documentation of tumor spread. The common use of the expression restaging only complicates the confusion with existing terminology, because patients may believe their cancer now has been defined as being of a different stage. Establishing more precise, universally accepted terminology for specific events that may occur during the cancer continuum and include several potential phases would help to enhance communication among oncologists, clinicians not focused on treating cancer, and patients. These terms could include observation; adjuvant, neoadjuvant, consolidation, and maintenance drug delivery; local, regional, and distant recurrences; and primary and multiples lines of antineoplastic therapy.

Similarly, the widely accepted common toxicity scales are focused on the periodic administration of antineoplastic agents that are often associated with sudden, sometimes severe, but generally intermittent effects that disappear or at least substantially improve prior to the next treatment course. Emesis, for example, is graded based on the severity of acute events beginning after the administration of an antiemetic agent. Even when therapy is delivered over several days, such as cisplatin given in a 5-day regimen in the treatment of germ cell tumors, the toxicity scale suggests that adverse effects will improve relatively rapidly or gradually over a period of hours, a few days, or several weeks in more severe circumstances.

But what happens when therapy becomes more chronic? This is increasingly the situation with maintenance strategies used in a variety of clinical settings, in which treatment is delivered 1 or more times a day for months or even years. Under these circumstances, what does it truly mean to state that a patient is experiencing low-grade nausea? Regarding intermittent drug delivery, such a symptom reported to last for several days on an every-3-week treatment cycle may be quite acceptable. But what if “low-grade nausea” occurs after each oral dose, and persists for several hours every day for as long as the drug is administered? Is it appropriate to use the same toxicity label to describe what patients are experiencing in this situation as with standard intermittent drug delivery?

The cancer staging system and toxicity scales have been enormously useful in the development of modern oncology, but perhaps it is time to consider modifications to reflect a substantially altered cancer clinical arena.
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.

### Treatment naive (n=39)

<table>
<thead>
<tr>
<th>RET Fusion-Positive NSCLC</th>
<th>RET Fusion-Positive Thyroid Cancer (Non-MTC)</th>
<th>RET-Mutant MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>85% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>100% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>73% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 70, 94)</td>
<td>(95% CI: 63, 100)</td>
<td>(95% CI: 62, 82)</td>
</tr>
<tr>
<td>0% CR + 85% PR</td>
<td>12.5% CR + 88% PR</td>
<td>11% CR + 61% PR</td>
</tr>
<tr>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR not yet reached</strong></td>
<td><strong>Median DoR not yet reached</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE); median follow-up: 7.4 months</td>
<td>(95% CI: NE); median follow-up: 8.8 months</td>
<td>(95% CI: NE); median follow-up: 17.5 months</td>
</tr>
</tbody>
</table>

### Previously treated (n=19)

<table>
<thead>
<tr>
<th>RET Fusion-Positive NSCLC</th>
<th>RET Fusion-Positive Thyroid Cancer (Non-MTC)</th>
<th>RET-Mutant MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>64% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>79% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>69% ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(95% CI: 54, 73)</td>
<td>(95% CI: 63, 94)</td>
<td>(95% CI: 65, 81)</td>
</tr>
<tr>
<td>1.9% CR + 62% PR</td>
<td>5.3% CR + 74% PR</td>
<td>9% CR + 60% PR</td>
</tr>
<tr>
<td><strong>Median DoR was 17.5 months</strong></td>
<td><strong>Median DoR was 18.4 months</strong></td>
<td><strong>Median DoR was 22.0 months</strong></td>
</tr>
<tr>
<td>(95% CI: 12, NE); median follow-up: 12.1 months</td>
<td>(95% CI: 75, NE); median follow-up: 17.5 months</td>
<td>(95% CI: NE, NE); median follow-up: 7.8 months</td>
</tr>
</tbody>
</table>

### Responses in intracranial lesions were observed in 10 of 11 previously treated patients with measurable brain metastases<sup>12</sup>

CNS DoR was ≥6 months in all responders with measurable brain metastases<sup>12</sup>

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

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### Find RET. Find results on Retevmo.com.

### Adverse Reactions and Laboratory Abnormalities

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

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

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

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

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**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=59) and previously treated patients (n=105) who had progressed on platinum-based chemotherapy with metastatic RET fusion-positive NSCLC, systemic therapy-naive (n=81) and previously treated (n=100) 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.

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

*Primary tumor histologies included papillary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, and Hurthle cell thyroid cancer.<sup>1</sup>

- Patients previously treated with platinum-based chemotherapy and with measurable CNS lesions at baseline according to IRC assessment.<sup>1</sup>

- Patients in this cohort received no prior systemic therapy other than radioactive iodine (RAI).<sup>1</sup>

- Patients in this cohort received a prior systemic therapy (including sorafenib, lenvatinib, or both) other than RAI.<sup>1</sup>

- The efficacy of Retevmo was evaluated in 75 patients with RET-mutant advanced MTC who were previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.<sup>1</sup>

- Patients with advanced or metastatic RET fusion-positive NSCLC who had progressed on platinum-based chemotherapy and those without prior systemic therapy were enrolled in separate cohorts.<sup>1</sup>

- Non-medullary thyroid cancers (non-MTC) by histology included papillary (n=51), poorly differentiated (n=4), anaplastic (n=2), and Hurthle cell (n=1).<sup>1</sup>

- Other tumors included pancreatic cancer (n=7), colon cancer (n=5), and adrenal gland carcinoma (n=3).<sup>1</sup>

- Number of patients included in the initial efficacy analysis. Efficacy was based on patients who had at least 6 months of follow-up.<sup>1</sup>

- Efficacy was evaluated in 105 adult patients with metastatic RET fusion-positive NSCLC who were previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001. At 105 patients received systemic therapy, 58 of the 105 patients received a prior multikinase inhibitor (MKI).<sup>1</sup>

- Patients with RET-mutant NSCLC and RET-mutant thyroid cancer (non-MTC) were not enrolled in the trial since RET is not the driver of tumor growth in these cancers.<sup>1</sup>

**BID=twice daily; CI=confidence interval; CNS=central nervous system; CR=complete response; DOQ=duration of response; NE=not estimable; ORR=objective response rate; PO=orally; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.**
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 transaminis. 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 embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

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

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

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

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (27%), hypertension (35%), 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 bilirubin (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 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 [ClCr] <30 mL/min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or end-stage renal disease.

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

SE HCP ISL_A1L_25AUG2020

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

References:
RETEVIMO™ (selpercatinib) capsules, for oral use

Initial U.S. Approval: 2020

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

INDICATIONS AND USAGE
RETEVIMO (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-mutated 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 to treat medically 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 2.8% of patients treated with RETEVIMO. Increased AST occurred in 5% 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 8%. 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 RETEVIMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Without, reduce dose or permanently discontinue RETEVIMO 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, 4.4% 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 RETEVIMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVIMO. 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 RETEVIMO based on the severity.

QT Interval Prolongation
RETEVIMO can cause concentration-dependent QT interval prolongation. An increase in QTcF interval to >550 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. RETEVIMO has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infection.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradycardia/arrhythmias, 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 RETEVIMO and during treatment.

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

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

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

Hypersensitivity
Hypersensitivity occurred in 4.3% of patients receiving RETEVIMO, 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 RETEVIMO and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume RETEVIMO at a reduced dose and increase the dose of RETEVIMO 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 RETEVIMO for recurrent hypersensitivity.

RETEVIMO™ (selpercatinib) capsules, for oral use

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVIMO (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37</td>
</tr>
<tr>
<td>Constipation</td>
<td>25</td>
</tr>
<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
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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, RETEVIMO has the potential to adversely affect wound healing.

Withhold RETEVIMO 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 RETEVIMO 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, RETEVIMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposure that were approximately equivalent to those observed at the recommended human dose of 160 mg orally twice daily resulted in embryopathy 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 RETEVIMO 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.


References: 1.

Table 1 summarizes the adverse reactions in LIBRETTO-001.

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

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</tr>
<tr>
<td>Vascular</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>35</td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥15%) in Patients Who Received RETEVIMO in LIBRETTO-001 (Cont.)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RETEVIMO (m=702)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>33</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>17</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>15</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

1 Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence.
2 Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain.
3 Fatigue includes fatigue, asthenia, malaise.
4 Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral edema, scrotal swelling, swelling face, eye swelling, peripheral swelling.
5 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbiliform, rash pruritic.
6 Headache includes headache, sinus headache, tension headache.
7 Includes cough, productive cough.
8 Includes dyspnea, dyspnea exertional, dyspnea at rest.
9 Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematoma, hemorrhagic cyst, hematoma, hemorrhagic cyst, hemorrhagic diathesis, hematuria, hemoptysis, hemorrhage, hemosiderinuria, intracranial hemorrhage, subarachnoid hemorrhage, subdural hematoma, spontaneous hematoma, hemorrhage, hematochezia, subdural hemorrhage.
10 Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbiliform, rash pruritic.

Only includes a grade 3 adverse reaction.

Clinically relevant adverse reactions in ≥15% of patients who received RETEVIMO 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 RETEVIMO in LIBRETTO-001

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RETEVIMO†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1-4 (%)</td>
<td>Grades 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>Chemistry</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>Hematology</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 RETEVIMO 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 RETEVIMO

Acid-Reducing Agents

Concomitant use of RETEVIMO with acid-reducing agents decreases selpercatinib plasma concentrations, which may reduce RETEVIMO anti-tumor activity. Avoid concomitant use of PPIs, H2 receptor antagonists, and locally acting antacids with RETEVIMO. If coadministration cannot be avoided, take RETEVIMO 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 RETEVIMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of RETEVIMO adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVIMO. If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, reduce the RETEVIMO dosage and monitor the QT interval with ECGs more frequently.

Strong and Moderate CYP3A Inducers

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

Effects of RETEVIMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETevaMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVIMO with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVIMO 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

RETevaMO 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, RETEVIMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVIMO 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. A study in pregnant monkeys supports the findings from animal studies, and its mechanism of action, RETEVIMO can cause fetal harm when administered to a pregnant woman. No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance of 30 to 59 mL/min). No dosage modification is recommended for patients with severe renal impairment (creatinine clearance <30 mL/min). No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST/total bilirubin ratio of 3 to 10 times upper limit of normal (ULN) and any AST) or severe (total bilirubin greater than 3 to 10 times ULN, or total bilirubin greater than 10 times ULN) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST/total bilirubin ratio of 3 to 10 times ULN and any AST) or severe (total bilirubin greater than 3 to 10 times ULN, or total bilirubin greater than 10 times ULN) hepatic impairment.

Of 702 patients who received RETEVIMO, 34% (239 patients) were ≥ 65 years of age and 10% (70 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVIMO between these age groups, although other concomitant medications used were generally more frequent in patients ≥ 75 years of age compared to younger patients.

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 fetsuses across the 2 litters. All viable fetsuses 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 potential 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 RETEVIMO and for 1 week after the final dose.

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 86MV2020

RETEVIMO™ (selpercatinib) capsules, for oral use

SE HCP BS 86MV2020
Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryo/fetal harm and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily.

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

Pediatric Use

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

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

Animal Toxicity Data

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

Geriatric Use

Of 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.

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SE HCP BS 08MAY2020

RETEVMO™ (selpercatinib) capsules, for oral use SE HCP BS 08MAY2020
Trastuzumab Deruxtecan Adds Indication for HER2+ Gastric Adenocarcinomas

The FDA has approved fam-trastuzumab deruxtecan-nxki (Enhertu) for the treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a previous trastuzumab (Herceptin)-based regimen.

Data from the phase 2 DESTINY-Gastric01 trial (NCT03329690) demonstrated that treatment with the antibody-drug conjugate resulted in an improvement in overall survival compared with irinotecan or paclitaxel, at 12.5 months (95% CI, 9.6-14.3) versus 8.4 months (95% CI, 6.9-10.7), respectively (HR, 0.59; 95% CI, 0.39-0.88; P = .0097). The objective response rate in patients treated with trastuzumab deruxtecan (n = 126) was 40.5% (95% CI, 31.8%-49.6%) compared with 11.3% (95% CI, 4.7%-21.9%) for those receiving irinotecan or paclitaxel (n = 62). Median progression-free survival was 5.6 months (95% CI, 4.3-6.9) versus 3.5 months (95% CI, 2.0-4.3), respectively. The median duration of response was 11.3 months (95% CI, 5.6-not reached) versus 3.9 months (95% CI, 3.0-4.9), respectively.

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Pembrolizumab/Chemo Moves Forward for Esophageal/GEJ Cancer
The FDA has granted a priority review to pembrolizumab (Keytruda) in combination with platinum- and fluoropyrimidine-based chemotherapy as a first-line treatment in patients with locally advanced unresectable or metastatic esophageal and gastroesophageal junction (GEJ) cancer.

The application is based on data from the phase 3 KEYNOTE-590 trial (NCT03189719), which showed that the frontline regimen significantly improved patients’ overall survival (OS) and progression-free survival (PFS) rates versus chemotherapy alone.

Results presented during the European Society for Medical Oncology Virtual Congress 2020 showed that the median OS with the chemoimmunotherapy regimen was 12.4 months versus 9.8 months with chemotherapy alone (HR, 0.73; 95% CI, 0.62-0.86; P < .0001). The OS rates at 12 months were 51% versus 39%, respectively, and 28% versus 16%, respectively, at 24 months.

Additionally, the median PFS per investigator assessment and RECIST v1.1 criteria was 6.3 months and 5.8 months with pembrolizumab/chemotherapy and chemotherapy alone, respectively (HR, 0.65; 95% CI, 0.55-0.76; P < .0001). The 12-month PFS rates were 25% versus 12% in the investigative and control arms, respectively, and the rates at 18 months were 16% versus 6%, respectively.

The FDA is expected to make a decision by April 13, 2021.

FDA Defers Action on BLA for Bevacizumab Biosimilar MYL-14020
Due to the FDA’s inability to complete an inspection of a manufacturing facility because of travel restrictions resulting from the coronavirus disease 2019 pandemic, the agency deferred action on the biologics license application (BLA) for the proposed bevacizumab (Avastin) biosimilar MYL-14020.

Codeveloped by Mylan NV and Biocon Ltd, MYL-14020 was approved by the Drug Controller General of India under the trade name Abemvy. The biosimilar was approved at injectable doses of 100 mg and 400 mg for all indications of the reference bevacizumab as part of specific regimens in patients with metastatic colorectal cancer, non–small cell lung cancer, glioblastoma, cervical cancer, and renal cell carcinoma.

The Indian approval was based on a comprehensive data package that confirmed the biosimilarity of MYL-14020 and bevacizumab, which included information from analytical, pharmacokinetic, and pharmacodynamic studies. The package also considered data from a randomized, double-blind study in Indian patients with colorectal cancer.

The BLA for MYL-14020 had previously been accepted by the FDA in March 2020, with a planned action date of December 27, 2020.

Darolutamide Gets Label Update for Nonmetastatic CRPC
The FDA has approved a supplemental new drug application, adding overall survival (OS) and other secondary end point data, for darolutamide (Nubeqa) in the treatment of patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).

The data were added to the prescribing information from the phase 3 ARAMIS trial (NCT02200614), which found that darolutamide reduced the risk of death by 31%, extending survival for nmCRPC patients (HR, 0.69; 95% CI, 0.53-0.88; P = .003). Additional findings included time to pain progression (HR, 0.65; 95% CI, 0.53-0.79; P < .0001) and time to initiation of cytotoxic chemotherapy (HR, 0.58; 95% CI, 0.44-0.76; P < .0001).

Darolutamide, an androgen receptor inhibitor, was approved by the FDA in July 2019 for the treatment of patients with nmCRPC using data from ARAMIS. The prescribing information was also updated to incorporate additional guidance on drug interactions. Final analysis of the trial reinforced darolutamide’s safety profile with an extended median 29 months’ follow-up for the overall study population.

Ibrutinib Label to Include Long-Term Waldenström Macroglobulinemia Data
The FDA has updated the prescribing information for ibrutinib (Imbruvica) to include safety and efficacy data for the agent in combination with rituximab (Rituxan) in the treatment of patients with Waldenström macroglobulinemia.

The update was based on findings from a final analysis of the phase 3 iNNOVATE trial (NCT02165397), in which the use of the combination led to significantly higher rates of progression-free survival (PFS) than the use of placebo plus rituximab, in patients who were treatment naïve and in those with disease recurrence.

In a five-year analysis for the 75 patients treated in each arm, investigators reported that at a median follow-up of 54 months, PFS had not yet been reached with the regimen (95% CI, 57.7-not estimable), whereas PFS was 20.3 months (95% CI, 13.0-27.6) with single-agent rituximab (HR, 0.25; 95% CI, 0.15-0.42; P < .0001). The 54-month PFS rates were 68% versus 25%, respectively.

Further, the median time to next treatment was not reached with ibrutinib and was 18 months with rituximab; 87% of patients receiving ibrutinib and 29% receiving rituximab had not received subsequent treatment at 54 months.

FDA Review of Liso-cel BLA for Relapsed/Refractory LBCL Is Still Ongoing
A decision on the biologics license application (BLA) for liso-cabtagene maraleucel (liso-cel), a chimeric antigen receptor T-cell product, in adult patients with relapsed/refractory large B-cell lymphoma (LBCL) who have undergone at least 2 previous therapies has not been reached by the FDA. The decision date for liso-cel was set for August 17, 2020, but was extended for 3 months to allow for additional analysis of data supplied by Bristol Myers Squibb.

The application is based on data from the phase 1 TRANSCEND-NHL-001 trial (NCT02631044). The trial demonstrated that liso-cel induced an objective response rate of 73% and a complete response (CR) rate of 53%. Time to first CR or partial response was a median of 1 month.

Data presented during the 2019 American Society of Hematology Annual Meeting and Exposition showed that the median progression-free survival reached with liso-cel was 6.8 months (95% CI, 3.3-14.1) and that 44% of patients were free of disease progression at the time of the presentation. The median overall survival was 21.1 months (95% CI, 13.3-not reached). After 1 year, 58% of patients who received liso-cel were still alive, with 86% experiencing a CR.

The FDA has not yet provided a new action date for the BLA.

TO READ MORE, VISIT https://bit.ly/3b79EwY.

TO READ MORE, VISIT https://bit.ly/3sEKgVM.


FORGE AHEAD WITH A BOLD APPROACH

Target BCMA for RRMM

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

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

Learn more at BLENREPHCP.com
**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

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

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

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

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

**Thrombocytopenia:** Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

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

**Embryo-Fetal Toxicity:** Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

**ADVERSE REACTIONS**

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 19% received a liquid formulation (not the approved dosage form) rather than the lyophilized powder.

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

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

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

**USE IN SPECIFIC POPULATIONS**

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

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

**Geriatric Use:** Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the 95 patients who received BLENREP at the 2.5-mg/kg dose, keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older.

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

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

The following is a brief summary only; see full Prescribing Information for complete product information.

### 1 INDICATIONS AND USAGE

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

This indication is approved under accelerated approval based on response rate as determined by the proportion of patients achieving minimal residual disease negativity following therapy.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 169), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

**Keratopathy**

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

**Visual Acuity Changes**

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

**Monitoring and Patient Instruction**

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

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

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

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

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

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

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

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

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

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

\(^a\) Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.

\(^b\) Visual acuity changes were determined upon eye examination.

\(^c\) Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

\(^d\) Dry eyes included dry eye, ocular discomfort, and eye pruritus.

\(^e\) Fatigue included fatigue and asthenia.

\(^f\) Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

\(^g\) Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

- **Eye Disorders:** Photophobia, eye irritation, infective keratitis, ulcerative keratitis.
- **Gastrointestinal Disorders:** Vomiting.
- **Infections:** Pneumonia.
- **Investigations:** Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
<td>22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
<td>2</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
<td>2</td>
</tr>
</tbody>
</table>

### 6.2 Immunogenicity

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

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

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nondiclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

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

**Data**

**Animal Data:** Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].

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

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].

BLENREP REMS

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

• Patients must complete the enrollment form with their provider.

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

Thrombocytopenia

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

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

• Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].

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

• Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1) of full Prescribing Information].

Lactation

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

Infertility

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

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including by use of Pottelligent technology licensed from BioWa, Inc.

For:

GlaxoSmithKline

Research Triangle Park, NC 27709

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August 2020 BRP:1BRS

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BLMADV190001 January 2021

Produced in USA.
2020 Approvals Expand Access to Care for Patients Across Tumor Types

IN A YEAR MARKED BY collaboration and innovation, therapeutic developments in oncology care once again dominated the novel drug approvals in 2020. In total, 21 novel agents were approved across hematologic/oncology, including 3 diagnostic imaging agents for the treatment of patients with breast cancer, prostate cancer, and neuroendocrine tumors, respectively. Additionally, new formulations and expanded indications and biosimilar approvals across tumor types opened up the accessibility of agents for patient populations, including reduced time in the clinic.

Such approvals included subcutaneous dasatumumab (Darzalex) plus hyalurondase-fihj [Darzalex Faspro], which reduces the administration time from hours for intravenous dasatumumab to minutes for patients with multiple myeloma. Additionally, the fixed-dose combination of pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo) was approved, providing an outpatient treatment option patients with HER2-positive breast cancer. Further, the approval of the novel oral formulation of decitabine and cedazuridine (Inqovi), marked the first noninvasive treatment for patients with myelodysplastic syndromes (MDS).1,2

The year 2020 was a decidedly promising one for patients with lung cancer, in particular those with non–small cell lung cancer (NSCLC). Specifically, the FDA approved 3 novel agents for patients with NSCLC and expanded the indication of 6 other agents. Two agents, selipercinatib (Retevmo) and pralsetinib (Gavreto), were approved for patients harboring RET mutations and for patients with indications that include medullary thyroid cancer (MTC).1

Approvals in other rare cancers also shared the spotlight in 2020, including those for gastrointestinal stromal tumors (GIST), a malignancy that affects the walls of the digestive system. The first, avapritinib (Ayvakit), joined 3 other targeted agents for the treatment of patients with this disease. The second, ripretinib (Qinlock), became the first agent approved in the fourth line for those patients who have exhausted all approved treatment options.1,2

The 21 novel agents approved across hematologic/oncology, in chronological order, are the following:

Avapritinib (Ayvakit) for adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including D842V mutations;

Tazemetostat (Tazverik) for adults and pediatric patients 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection;

Isatuximab-irfc (Sarcilisa) in combination with pomalidomide (Pomalyst) and dexamethasone for adult patients with multiple myeloma who have received at least 2 prior therapies, including lenalidomide (Revlimid) and a proteasome inhibitor;

Selumetinib (Koselugo) for pediatric patients 2 years and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas;

Tucatinib (Tukysa) in combination with trastuzumab (Herceptin) and capecitabine for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received 1 or more prior anti-HER2–based regimens in the metastatic setting;

Pemigatinib (Pemazyre) for the treatment of adults with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, as detected by an FDA-approved test;

Sacituzumab govitecan-hziy (Trodelvy) for adult patients with metastatic triple-negative breast cancer who received at least 2 prior therapies for metastatic disease;

Capmatinib (Tabrecta) for adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping, as detected by an FDA-approved test;

Selipercinatib (Retevmo) for 3 indications: adult patients with metastatic RET fusion–positive NSCLC, adults and pediatric patients at least 12 years of age with advanced or metastatic RET-mutant MTC who require systemic therapy, and adults and pediatric patients at least 12 years of age with advanced or metastatic RET fusion–positive thyroid cancer that has stopped responding to radioactive iodine therapy or is not appropriate for radioactive iodine therapy;

Ripretinib (Qinlock) for adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib (Gleevec);

Fluoroestradiol F 18 (Geriana) for the visual detection of estrogen receptor–positive lesions on positron emission tomography (PET) scan images in addition to tissue biopsy in patients with recurrent or metastatic breast cancer;

Lurbinectedin (Zepzelca) for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy;

Decitabine plus cedazuridine (Inqovi), an oral combination for adult patients with MDS including previously treated and untreated de novo and secondary MDS with French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups;

Tafasitamab-cxix (Monjuvi), a CD19-directed cytolytic antibody, indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low-grade lymphomas, and who are not eligible for autologous stem cell transplant;

Belantamab mafodotin-blmf (Blenrep) for adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent;
Copper Cu 64 dotate (Detectnet) injection for the detection of somatostatin receptor–positive neuroendocrine tumors in adults;

Pralsetinib (Gavreto) for adult patients with metastatic RET fusion–positive NSCLC as detected by an FDA-approved test;

Naxitamab-gqgk (Danyelza) in combination with granulocyte-macrophage colony-stimulating factor for pediatric patients 1 year and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow demonstrating a partial or minor response to or stable disease with prior therapy;

Galium 68 PSMA-11, a radiative diagnostic agent that is administered in the form of an intravenous injection for PET imaging of prostate-specific membrane antigen–positive lesions in men with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy and with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen levels;

Margertuximab-cmkb (Margenza) in combination with chemotherapy for the treatment of adult patients with metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2 regimens, at least 1 of which was for metastatic disease; and

Relugolix (Orgovyx), the first oral gonadotropin-releasing hormone receptor antagonist for adult patients with advanced prostate cancer.

NEW INDICATIONS

The FDA granted approval for the following indications:

Pembrolizumab (Keytruda) for patients with BCG-unresponsive, high-risk, non–muscle-invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy;

Neratinib (Nerlynx) in combination with capecitabine for adult patients with advanced or metastatic HER2–positive breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting;

Nivolumab (Opdivo) plus ipilimumab (Yervoy) for patients with hepatocellular carcinoma who have not received prior systemic therapy;

Durvalumab (Imfinzi) in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage SCLC;

Luspatercept-aamt (Reblozyl) for the treatment of patients with anemia that failed to respond to an erythropoiesis-stimulating agent and required 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk MDS with ringed sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ringed sideroblasts and thrombocytosis;

Encorafenib (Braftovi) in combination with cetuximab (Erbitux) for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy;

Mitomycin gel (Jelmyto) for adult patients with low-grade upper tract urothelial cancer;

Ibrutinib (Imbruvica) in combination with rituximab (Rituxan) for the initial treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma;

Niraparib (Zejula) for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a complete or partial response to first-line platinum-based chemotherapy;

Daratumumab plus hyaluronidase-fihj (Darzalex Faspro) for adult patients with newly diagnosed or relapsed/refractory multiple myeloma;

Olaparib (Lynparza) in combination with bevacizumab (Avastin) for first-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency–positive status, defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability;

Pomalidomide (Pomalyst) for adult patients with AIDS-related Kaposi sarcoma after failure of highly active antiretroviral therapy and Kaposi sarcoma in adult patients who are HIV negative;

Rucaparib (Rubraca) for patients with deleterious BRCA mutation (germline and/or somatic)–associated metastatic castration-resistant prostate cancer who have been treated with androgen receptor–directed therapy and a taxane-based chemotherapy;

Nivolumab plus ipilimumab as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 at least 1%, as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations;

Atezolizumab (Tecentriq) for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells or PD-L1 stained tumor-infiltrating immune cells covering ≥ 10% of the tumor area), with no EGFR or ALK genomic tumor aberrations;

Olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated metastatic castration-resistant prostate cancer who have progressed following prior treatment with enzalutamide (Xtandi) or abiraterone acetate (Zytiga);

Brigatinib (Alunbrig) for adult patients with ALK–positive metastatic NSCLC as detected by an FDA-approved test;

Nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC with no EGFR or anaplastic ALK genomic tumor aberrations;

Atezolizumab plus bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy;

Ramucirumab (Cyramza) in combination with erlotinib (Tarceva) for first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 mutations;

Nivolumab for patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy;

Gemcitabine plus oxolamine (Mylotarg) for newly diagnosed CD33+ acute myeloid leukemia in pediatric patients 1 month and older;

Pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor

CONTINUED ON PAGE 28
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- Therapeutic sequencing in shifting treatment landscapes
- Clinical and economic advantages associated with preclinical lymphedema detection and prevention of clinical lymphedema

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mutational burden–high (≥ 10 mutations per megabase) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options;  
**Tazemetostat** for adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients who have no satisfactory alternative treatment options;  
**Selinexor (Xpovio)** for adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy;  
**Pembrolizumab** for patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation;  
**Fixed-dose combination of pertuzumab (Perjeta), trastuzumab, and hyaluronidase-zzxf (Phesgo)** for subcutaneous injection in combination with chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer; in combination with chemotherapy for the adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence; and in combination with docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease;  
**Pembrolizumab** for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high or mismatch repair–deficient colorectal cancer;  
**Avelumab (Bavencio)** for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy;  
**Atezolizumab in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf)** for patients with BRAF V600 mutation–positive unresectable or metastatic melanoma;  
**Carfilzomib (Kyprolis) and daratumumab (Darzalex)** in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 lines of therapy;  
**Azacitidine tablets (Onureg)** for continued treatment of patients with acute myeloid leukemia who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and are not able to complete intensive curative therapy;  
**Nivolumab plus ipilimumab** as first-line treatment for adult patients with unresectable malignant pleural mesothelioma;  
**Pembrolizumab** for adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) and pediatric patients with refractory cHL or cHL that has relapsed after 2 or more lines of therapy;  
**Venetoclax (Venclexta)** in combination with azacitidine, decitabine, or low-dose cytarabine for newly diagnosed acute myeloid leukemia in adults 75 years or older or who have comorbidities precluding intensive induction chemotherapy;  
**Pembrolizumab** in combination with chemotherapy for the treatment of patients with locally recurrent, unresectable, or metastatic triple-negative breast cancer whose tumors express PD-L1 (combined positive score, ≥ 10) as determined by an FDA approved test;  
**Pralsetinib** for adults and pediatric patients 12 years and older with advanced or metastatic RET-mutant MTC who require systemic therapy or RET fusion–positive thyroid cancer who require systemic therapy and who are refractory to radioactive iodine (if radioactive iodine is appropriate);  
**Selinexor in combination with bortezomib (Velcade) and dexamethasone** for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy; and  
**Osimertinib (Tagrisso)** for adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations.  

### CELL THERAPY

**Breuxucabtagene autoleucel (Tecartus),** a CD19-directed genetically modified autologous T-cell immunotherapy, was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

### BIOSIMILARS

**Pegfilgrastim-afgp (Nyevepra)** was approved as a biosimilar to the reference product pegfilgrastim (Neulasta) and is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

**Rituximab-arrx (Riabni)** was approved as a biosimilar to the reference product rituximab and is indicated for the treatment of adult patients with non-Hodgkin lymphoma (NHL), specifically those with relapsed or refractory, low-grade or follicular, CD20+ B-cell NHL as a single agent; previously untreated follicular, CD20+, B-cell NHL in combination with first-line chemotherapy and in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy; nonprogressing (including stable disease), low-grade, CD20+, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy; previously untreated diffuse large B-cell, CD20+ NHL in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone or other anthracycline-based chemotherapy regimens. It also is approved for adults with previously untreated and treated CD20+ CLL in combination with fludarabine and cyclophosphamide; and for granulomatosis with polyangiitis and microscopic polyangiitis in adult patients in combination with glucocorticoids.

For a full list of references, see the article at [Onclive.com](http://Onclive.com).
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RELUGOLIX (ORGOVYX) RAPIDLY SUPPRESSES testosterone (T) levels in men with advanced prostate cancer with a markedly lower risk of cardiovascular events than leuprolide, paving the way for a new hormonal therapy for this population. In December 2020, the drug became the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist to gain FDA approval.1

The FDA approved relugolix based on data from the phase 3 HERO trial (NCT03085095) in men who required at least 1 year of androgen deprivation therapy (ADT) with either prostate cancer recurrence following radiation or surgery or newly diagnosed castration-sensitive advanced disease. Participants were randomly assigned to a loading dose of oral relugolix 360 mg on the first day followed by daily doses of 120 mg or 22.5 mg of leuprolide, a luteinizing hormone-releasing hormone (LHRH) agonist, administered via subcutaneous injection every 3 months for 48 weeks.1

Investigators found that 96.7% (95% CI, 94.9%-97.9%) of patients who received relugolix (n = 622) achieved and maintained serum T at castration levels (< 50 ng/dL) through 48 weeks compared with 88.8% (95% CI, 84.6%-91.8%) of those who received leuprolide (n = 308).2 Further, relugolix was associated with a significant reduction in major adverse cardiovascular events (MACE) compared with leuprolide in patients with advanced disease after 48 weeks of treatment (2.9% vs 6.2%, respectively).2

Currently available medical ADT options, which include LHRH agonists such as leuprolide and goserelin, have been a mainstay of treatment for men with advanced prostate cancer but are only available in injectable formulations and are associated with an elevated risk of cardiovascular disease, according to an FDA review of the relugolix application. Degarelix (Firmagon), the only GnRH receptor antagonist available for prostate cancer treatment in the United States before the relugolix approval, is also an injectable formulation.3

In an interview with OncologyLive®, Neal D. Shore, MD, lead investigator for the HERO trial, explained how relugolix could affect the standard of care for men with advanced prostate cancer. Shore is medical director of the Carolina Urologic Research Center in Myrtle Beach, South Carolina. In early January 2021, he prescribed relugolix for the first time post approval to treat a 77-year-old man with advanced disease who displayed cardiovascular risk factors.

**What is the clinical utility for relugolix compared with standard-of-care LHRH agonists?**

At the end of 48 weeks, we looked at testosterone recovery in roughly 184 patients in both arms who finished treatment. Fifty-three percent of the relugolix patients were back to normal testosterone levels, ostensibly eugonadal, and only 3% of the LHRH agonist patients were back to being eugonadal at 90 days. This is really a nice advantage—the faster recovery for patients who may consider intermittent ADT or who may be on a shorter course of 6 to 12 months for adjuvant/neoadjuvant radiation therapy strategies.

This is the only oral testosterone suppressive medication demonstrated in a phase 3 global trial to have met the efficacy end point of T suppression compared with the traditional LHRH agonist.

Now patients can receive an oral treatment, 1 pill once a day, instead of an intramuscular or subcutaneous injection. So there’s an obvious convenience for many patients. And, during a pandemic, I think it’s really nice that patients don’t have to come in and receive an injection—whether it’s intramuscular or subcutaneous. They don’t get exposed to infection and neither do the clinic staff.

**What’s the appropriate level of T suppression for these patients?**

We’ve been debating this issue for many years: How important is it to get testosterone suppression not just below 50 ng/dL, but below 20 ng/dL? And, also to do it very rapidly with the corollary PSA [prostate-specific antigen] declines? We met all of these in our secondary end points in a highly statistically significant way. In addition to meeting our primary and secondary end points of testosterone suppression in a convenient 1-pill-per-day dose, we met all the secondary end points of profound T suppression and with corollary PSA declines.

**How does relugolix compare for safety?**

When we looked at the safety analysis, we saw that the patients in the relugolix arm had fewer cardiovascular complications. In fact, we demonstrated a decrease of 54% compared with the LHRH agonist arm. This was a prespecified safety analysis. More than 90% of patients who start ADT—this was true in our study and has been observed in many other studies—have at least 1 cardiovascular risk factor. They may have hypertension, dyslipidemia, glucose dysregulation, prior myocardial infarctions [MI], or cerebrovascular events.

In particular, as it relates to MACE, we purposely excluded patients who had had a MACE, a nonfatal MI or cerebrovascular accident, or arrhythmia within 6 months of screening. Thus, we reduced the number of patients who had had a MACE to about 14% of those enrolled. That number at baseline is probably somewhere from 30% to 40%, depending upon where you practice.

Nonetheless, even though we purposefully reduced the number of patients who had a MACE, we demonstrated in those patients who received relugolix versus an LHRH agonist the likelihood of getting another MACE was approximately 5 times higher in the LHRH agonist arm.

**Which patients are candidates for relugolix therapy?**

I think that relugolix fits in the treatment decision making for all patients with prostate cancer who would benefit from testosterone suppression. The patient’s health care provider, whether it’s a medical oncologist, urologist, or radiation oncologist, should be fully aware of the approval of relugolix and why you would want to have a discussion regarding it versus an LHRH agonist or GnRH antagonists that are given parenterally. Patient-physician shared decision-making is key to optimizing cancer care.

**REFERENCES**

FDA approval—December 18, 2020
FDA grants approval for oral gonadotropin-releasing hormone (GnRH) receptor antagonist relugolix (Orgovyx) as a treatment for patients with advanced prostate cancer.

Mechanism of action:
• Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone and follicle-stimulating hormone, and consequently testosterone.

How supplied:
• 120-mg tablets

PIVOTAL CLINICAL TRIAL
HERO (NCT03085095), a randomized, open label study in men with androgen-sensitive advanced prostate cancer who require at least 1 year of continuous androgen-deprivation therapy and with biochemical or clinical relapse after primary intervention, including newly diagnosed castration-sensitive metastatic disease or advanced localized disease.

Efficacy results in the HERO trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained castration rate (95% CI)*</td>
<td>96.7% (94.9%-97.9%)</td>
<td>88.8% (84.6%-91.8%)</td>
</tr>
<tr>
<td>Between-group difference</td>
<td>7.9 percentage points (95% CI, 4.1%-11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Key secondary outcomes

- Testosterone recovery to at least 280 ng/dL at 90 days: 54.0% vs. 0.6%
- Cumulative probability of testosterone suppression day 4: 56.0% vs. 0.0%
- Cumulative probability of testosterone suppression day 15: 98.7% vs. 12.0%
- Probability of profound testosterone suppression (< 20 ng/dL) on day 15: 78.4% vs. 1.0%
- Patients with a confirmed PSA response* at day 15: 79.4% vs. 19.8%

*Sustained testosterone suppression was defined as concentrations less than 50 ng/dL from day 29 through week 48.

*PSA response was defined as a decrease of more than 50% in the PSA level.

Warnings and Precautions

- QT/QTc interval prolongation
- Embryo-fetal toxicity

Commonly reported adverse events in the HERO trial

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flush</td>
<td>54%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Cardiovascular end points

<table>
<thead>
<tr>
<th>Cumulative incidence of major cardiovascular adverse events</th>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.46 (95% CI, 0.24-0.88)</td>
<td></td>
</tr>
</tbody>
</table>

Baseline patient characteristics

<table>
<thead>
<tr>
<th>Median age (years, range)</th>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>72 (48-91)</td>
<td>71 (47-97)</td>
</tr>
</tbody>
</table>

Clinical disease presentation (%)

<table>
<thead>
<tr>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of biochemical or clinical relapse after local primary intervention with curative intent</td>
<td>22.7%</td>
</tr>
</tbody>
</table>
| Newly diagnosed androgen-sensitive metastatic disease | 27.7%
| Advanced localized disease not suitable for primary surgical intervention with curative intent | 51.3%

Median PSA level (%)

<table>
<thead>
<tr>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PSA level (ng/mL)</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Cardiovascular risk factors (%)

<table>
<thead>
<tr>
<th>Relugolix (n = 622)</th>
<th>Leuprolide (n = 308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular or cerebrovascular risk factors</td>
<td>94.2</td>
</tr>
<tr>
<td>History of major adverse cardiovascular events</td>
<td>82.5</td>
</tr>
</tbody>
</table>

References

Surge of New Drugs Fuels Optimism in Pediatric Oncology

by MEIR RINDE

THE LANDSCAPE FOR PEDIATRIC oncology drugs expanded dramatically last year, with 8 new drugs or indications specifically approved for children compared with just 47 for treatment and supportive care products from the early 1950s through 2019.1,2

The roster of 2020 therapies includes a rare example of a pediatric-only agent, selumetinib (Koselugo), which was approved for neurofibromatosis type 1 (NF1) with inoperable plexiform neurofibromas (PNs), as well as treatments for thyroid cancer, Hodgkin lymphoma, neuroblastoma, acute myeloid leukemia (AML), epithelioid sarcoma, and tumor mutational burden (TMB)-high solid tumors. This year began with additional progress: On January 14, 2021, the FDA approved a new indication for crizotinib (Xalkori) for patients 1 year and older and young adults with relapsed or refractory systemic ALK-positive anaplastic large cell lymphoma.3 (TIMELINE)

Pediatric oncologists attribute the burst of approvals to advances in genomics and immuno-oncology that have sped up development of targeted therapies, an increasing willingness to treat adolescents with drugs approved for adults, and regulatory efforts such as the Creating Hope Act of 2012, which gives incentives to pharmaceutical companies to develop pediatric treatments. The pace of approvals is expected to increase further thanks to the Research to Accelerate Cures and Equity (RACE) for Children Act, which requires drugmakers to investigate potential pediatric applications of

**TIMELINE. Recent FDA Approvals for Pediatric Indications**

<table>
<thead>
<tr>
<th>2021</th>
<th>2020</th>
<th>November 25</th>
<th>October 14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>January 14</strong></td>
<td><strong>December 1</strong></td>
<td><strong>November 25</strong></td>
<td><strong>October 14</strong></td>
</tr>
<tr>
<td>Crizotinib (Xalkori) Patients 1 year and older and young adults with ALK-positive relapsed or refractory, systemic anaplastic large cell lymphoma</td>
<td>Pralsetinib (Gavreto) Adults and pediatric patients 12 years and older with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy or RET fusion-positive thyroid cancer who require systemic therapy and are refractory to radiiodine, if appropriate</td>
<td>Naxitamab-gqgk (Danyelza) In combination with granulocyte-macrophage colony-stimulating factor for patients 1 year and older and adults with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have had a partial or minor response or stable disease after prior therapy</td>
<td>Pembrolizumab (Keytruda) Pediatric patients with classical Hodgkin lymphoma that is refractory or that has relapsed after 2 or more lines of therapy</td>
</tr>
</tbody>
</table>
new targeted therapies. The act, signed into law in August 2017, went into effect in August 2020.1

“Those incentives are really starting to align to encourage pharmaceutical companies to support pediatric studies and are driving this forward. We’re starting to see some of the results from that,” said Theodore W. Laetsch, MD, a pediatric oncologist who leads the Developmental Therapeutics Program and Very Rare Malignant Tumors Program at Children’s Hospital of Philadelphia in Pennsylvania. He also heads the rare tumor disease committee of the Children’s Oncology Group (COG), a National Cancer Institute (NCI)-supported clinical trials collaborative.

“The FDA is paying very close attention from the start of drug development. It’s helped a great deal,” said Elizabeth Fox, MD, MS, senior vice president for clinical trials research and associate director for clinical research at the Comprehensive Cancer Center of St Jude Children’s Research Hospital in Memphis, Tennessee. Thanks to the RACE for Children Act, “we are seeing a lot of interest from pharmaceutical companies in discussing what trials can be done in kids and how. It is achieving its initial goal—to start the conversation. Pharmaceutical companies are also starting to do basket trials for children. That is great for potential access to drugs.”

Although the FDA has approved fewer therapies for pediatric patients than for adults, the number of drugs indicated for children and teenagers has been growing as a result of federal legislation to promote development, starting with a 1997 law enacting a pediatric exclusivity provision, FDA officials said in a review published in Pediatric Blood & Cancer.1 From 1953 to 2019, the FDA approved 34 drugs covering 38 indications for treating childhood cancers and an additional 6 therapies for preventing or mitigating adverse effects.2 In 2019, that total grew by 3, with the approval of entrectinib (Rozlytrek) for adults and children with NTRK fusion-positive tumors; ruxolitinib (Jakafi) for adults and children 12 years and older with graft-versus-host disease; and an expanded indication for dalteparin sodium (Fragmin) for treating symptomatic venous thromboembolism in pediatric patients based on pivotal data that included participants with active cancers.3

One barrier to developing pediatric oncology drugs has been the exclusion of young patients from studies over concerns that an approval could be derailed if a child were harmed in the trial, Laetsch said. Those concerns turned out to be overblown, he said.

Further, with the field of precision medicine rapidly expanding, investigators have recognized that the same molecular drug targets were often present in both adult and pediatric cancers, said Donald Williams Parsons, MD, PhD, deputy director of Texas Children’s Cancer and Hematology Centers in Houston and COG study chair for the NCI-COG Pediatric MATCH study (NCT03155620). “There’s this recognition that it doesn’t make much sense for a company to be studying exclusively adults, if they have a target that’s also in children, for their financial self-interest and if they’re trying to identify rare groups. That’s a rare group—the kids—and one they can target,” Parsons said.

The approval of larotrectinib (Vitrakvi) in November 2018 for patients with NTRK fusion-positive solid tumors was a major step in efforts to boost the development of pediatric drugs. Although NTRK fusions are rare in cancers overall, they...
occur more frequently in some pediatric tumors, including 95.5% of infantile fi brosarcomas.4 Trial investigators recruited both adults and children early on and created an oral liquid formulation for the youngest patients.

“Almost one-third of the patients in the data set [N = 55] that was submitted to the FDA for approval were children. That’s really unusual for a drug that’s being approved for adult cancer. That highlighted to people involved in drug development that this can [not only] accelerate the pathway for children, but also get the drug approved for adults,” said Laetsch, who was lead author on the SCOUT trial (NCT02637687), 1 of 3 studies whose findings paved the way for the decision. 7,8

The development of selumetinib similarly demonstrated how molecular targeting broadens potential uses for an investigational agent. The MEK inhibitor previously had disappointing results in adult trials for non–small cell lung cancer (NSCLC), metastatic uveal melanoma, and thyroid cancer.9 Then the drug came to the attention of NCI investigators who for years had been studying potential treatments for NF1, a rare genetic disease that can lead to PNs and aggressive, malignant neural tumors.10

In 2011 they tested selumetinib in children with NF1 in PNs and observed tumor shrinkage. In the subsequent SPRINT phase 2 stratum 1 trial (NCT01362803) involving 50 children aged 3.5 to 17.4 years, the overall response rate (ORR) was 66% (95% CI, 51%-79%), comprising all confirmed partial responses, which lasted 12 months or longer for 82% of the responders.9 The FDA approved the drug for patients 2 years and older with NF1 who have symptomatic inoperable PNs and awarded AstraZeneca a voucher that can be used for a subsequent priority review for successfully developing a rare pediatric disease product.12

Like larotrectinib, selumetinib is an example of a narrowly targeted drug successfully matched to a small group of pediatric patients with an unmet need, Parsons said. NF1 “is a bad clinical problem for kids, and it’s a pretty specific population of patients,” he said. “Neurofibromatosis is a relatively common genetic disease by genetic disease standards, but by any other standards, it’s a rare disease. It’s a tumor type without other good available therapies, so specific trials were designed for those patients using the drug based upon the clinical research in that group.”

The FDA also awarded a priority review voucher to Y-mAbs Therapeutics, Inc, for developing naxitamab-gqgk (Danyelza), an anti-GD2 monoclonal antibody for the treatment of patients 1 year and older with relapsed or refractory high-risk neuroblastoma who have experienced a partial response or stable disease after prior therapy. The voucher was sold for $105 million in December 2020, a month after naxitamab was granted accelerated approval for use in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) for this patient population.13,14

In the phase 1/2 study 12-230 trial (NCT01757626), naxitamab in combination with GM-CSF resulted in an ORR of 34% (95% CI, 20%-51%), including a 26% complete response (CR) rate, in 38 patients. In the phase 2 study 201 trial (NCT03363373), the ORR with the combination was 45% (95% CI, 24%-68%) in 22 patients, with a CR rate of 36%. The median patient age in both trials was 5 years.14

### Table. Treatment Arms Enrolling Patients in Pediatric MATCH Trial 19

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecular target(s)</th>
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</thead>
<tbody>
<tr>
<td>Larotrectinib (Vitrakvi)</td>
<td>NTRK fusions</td>
</tr>
<tr>
<td>Erdafitinib (Balversa)</td>
<td>FGFR1/2/3/4 alterations</td>
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<tr>
<td>Tazemetostat (Tazverik)</td>
<td>EZH2 alterations or members of the SWI/SNF complex</td>
</tr>
<tr>
<td>Samotolisib (LY0323414)</td>
<td>TSC2 loss of function or PI3K/mTOR pathway activating mutations</td>
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<tr>
<td>Selumetinib (Koselugo)</td>
<td>Activating MAPK pathway mutations</td>
</tr>
<tr>
<td>Ensartinib</td>
<td>ALK or ROS1 alterations</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf)</td>
<td>BRAF V600 mutations</td>
</tr>
<tr>
<td>Olaparib (Lynparza)</td>
<td>Defects in DNA damage repair genes</td>
</tr>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>Activating alterations in cell cycle genes</td>
</tr>
<tr>
<td>Ulixertinib (BVD-523FB)</td>
<td>Activating MAPK pathway mutations</td>
</tr>
<tr>
<td>Ivosidenib (Tibsovo)</td>
<td>IDH1 mutations</td>
</tr>
<tr>
<td>Tipifarnib</td>
<td>HRAS mutations</td>
</tr>
<tr>
<td>Selercatinib (Retevmo)</td>
<td>RET alterations</td>
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</tbody>
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### Extending Adult Indications

Although selumetinib is a purely pediatric drug and naxitamab will be used primarily to treat children, most of the pediatric approvals in 2020 were based on positive findings in adult trials or were extensions of previous approvals for adult therapies. Three novel agents and 1 previously approved drug were granted pediatric approvals or indications based on trials that included only adult patients. The first RET inhibitors, selrecatinib (Retevmo) and pralsetinib (Gavreto), were approved for patients 12 years and older with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy, as well as patients with advanced or metastatic RET fusion–positive thyroid cancer who require systemic therapy and who are refractory to radioactive iodine, if appropriate. Both agents are also approved for adults with metastatic RET fusion–positive NSCLC.2 Tazemetostat (Tazverik), a first-in-class EZH2 inhibitor, was approved for adults and pediatric patients 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.2
The FDA also granted 2 new sets of indications for pembrolizumab (Keytruda) based on adult trials. One indication was for pediatric patients with refractory classical Hodgkin lymphoma (cHL) or cHL that has relapsed after 2 or more lines of therapy, as well as for adult patients with relapsed or refractory cHL, based on findings from trials in which the youngest patient was 18 years and the median age was 35 years. The second indication was for adult and pediatric patients who have unresectable or metastatic TMB-high (≥ 10 mutations per megabase) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. The median age in the pivotal phase 3 ALFA 0701 trial (NCT00927498), which enrolled patients from 50 to 70 years. The therapy had been previously approved as a single agent for patients 2 years and older with CD33+, relapsed/refractory AML.17

**THE NEXT WAVE**

A number of pediatric clinical trials are under way, but it is not yet evident which will contribute to the next wave of approvals for this population. That may become clearer when results are reported from COG’s Pediatric MATCH trial, a collaborative, nationwide screening protocol with multiple simultaneously ongoing single-agent, phase 2 treatment arms.

Each arm is testing an approved or investigational agent in a variety of tumors in children who have the matched molecular alteration targeted by the study drug. Of 357 patients whose tumor samples successfully underwent gene sequencing, 112 matched at least 1 of 10 treatment protocols then available (29%; 95% CI, 24%-33%), and 95 patients (24%; 95% CI, 20%-29%) were assigned to an arm, according to findings presented at the 2019 American Society of Clinical Oncology Annual Meeting.18

Pediatric MATCH began enrolling patients in 2017, and Parsons said the participating drug companies could soon begin using the findings in FDA applications. “They are clearly interested in obtaining the clinical trial data for their regulatory purposes. We are just getting to the point, over the next few months, where we’re completing enrollment on some of those study arms,” he said.

In its current format, Pediatric MATCH has 13 treatment arms enrolling patients, with plans to add 2 more cohorts. Each arm seeks to enroll at least 20 patients aged 1 to 21 years who have solid tumors including lymphomas, brain tumors, or histiocytoses that are resistant or recurrent on standard therapy. Many of the drugs being tested are approved in adult and/or pediatric indications (TABLE).19

In the cellular therapy space, hundreds of chimeric antigen receptor (CAR) T-cell studies and other types of novel therapeutics are under way. These include potential treatments for pediatric acute lymphoblastic leukemia (ALL) and pediatric mature B-cell non-Hodgkin lymphomas. An allogeneic CAR T-cell therapy for pediatric ALL is also being studied.

Other drugs being investigated for pediatric cancers include the investigational TRK inhibitor selitrectinib (BAY2731954), which is being evaluated for patients with NTRK fusion–positive solid tumors previously treated with this class of agents in a phase 1/2 trial (NCT03215511). Earlier hopes for the utility of immune checkpoint inhibitors were tamped down in the past 2 years by studies of pembrolizumab, nivolumab (Opdivo), and atezolizumab (Tecentriq) that found little activity in pediatric tumors other than Hodgkin lymphoma.20-22 Investigators are studying whether these agents may have more benefit in specific patient subgroups or in drug combinations.

Investigators are also trying to maximize the efficacy of previously approved treatments by stratifying patients, combining therapies, and testing sequencing strategies. St Jude’s Total Therapy XVII trial (NCT03117751), for example, is dividing children with newly diagnosed B-cell or T-cell ALL or acute lymphoblastic lymphoma into low-, standard-, and high-risk groups using clinical, immunophenotype, and genomic features. The study, which aims to enroll 1000 patients, will test multiple therapies as appropriate for 3 main phases: remission induction, consolidation, and continuation. The goal is to improve event-free survival rates.23

Even if Pediatric MATCH and other studies do find targetable molecular pathways in pediatric patients, much more work lies ahead, Parsons said. “Beyond inventing whatever’s new, the real challenge of the next 10, 20, 30 years [will be] figuring out how do we best use those [therapies], in which patients, and how do we incorporate [them] and combine [them] with a chemotherapy or radiotherapy that’s really effective for some patients,” he said.
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

**INDICATION**

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

**IMPORTANT SAFETY INFORMATION**

**WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA**

Fatle neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

**CONTRAINDICATION**

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

**WARNINGS AND PRECAUTIONS**

**Severe Neutropenia**

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

**Severe Diarrhea**

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

**Interstitial Lung Disease (ILD)**

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

**Severe Hypersensitivity Reactions**

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

**Embryo-Fetal Toxicity**

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

**ADVERSE REACTIONS**

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%,...
ONIVYDE® is a registered trademark of Ipsen Biopharm Ltd.

ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER**

* Liposomal irinotecan + 5-FU/LV is the only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.†,‡,³

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE†

- Proven in combination with 5-FU/LV in NAPOLI-1—the largest phase 3 trial in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy.³,⁴

DRUG INTERACTIONS

Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme-inducing therapies 22 weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors 21 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy and Reproductive Potential

Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

Lactation

Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

Pediatric

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

DOSE AND ADMINISTRATION

The recommended dose of ONIVYDE is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD. Do not substitute ONIVYDE for other drugs containing irinotecan HCl.


For more information, visit ONIVYDEinfo.com
ONIVYDE® (irinotecan liposome injection) for intravenous use

Initial U.S. Approval: 1996

BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

1. INDICATIONS AND USAGE
ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (see Dosing and Administration, 2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity. (see Dosing and Administration, 2.2, see Warnings and Precautions 5.2)

4 CONTRAINDICATIONS
ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosing and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset >24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea. In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

6 ADVERSE REACTIONS
The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia (see Warnings and Precautions, 5.1; Boxed Warning)
- Severe Diarrhea (see Warnings and Precautions, 5.2; Boxed Warning)
- Interstitial Lung Disease (see Warnings and Precautions, 5.3)
- Severe Hypersensitivity Reactions (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience
The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥20%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
ONIVYDE® is not indicated as a single agent for the management of metastatic colorectal cancer when the ANC is 1500/mm³ or above. Reduce the dose of ONIVYDE® periodically during treatment. (See Warnings and Precautions, 5.1; Boxed Warning, 1.1.7.1; Contraindications, 5.1.)

**WARNINGS AND PRECAUTIONS**

**ONIVYDE® is contraindicated in patients who have experienced a severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (≥5% difference Grades 3-4) or neutropenic sepsis.**

**Severe Hypersensitivity Reaction:**

Allergic and anaphylactic reactions have been reported with irinotecan, including anaphylaxis. Discontinue ONIVYDE® immediately and institute appropriate emergency procedures. Monitor for signs and symptoms of hypersensitivity reaction, including flushing, rash, urticaria, bronchospasm, laryngeal edema, cardiovascular collapse, and hypotension. ONIVYDE® can cause severe and life-threatening hypersensitivity reactions as well as fatal ILD. If a patient experiences an allergic reaction with ONIVYDE®, discontinue treatment with irinotecan, discontinue ONIVYDE®, and institute appropriate emergency procedures.

**Severe or Life-Threatening Neutropenia:**

Severe or life-threatening neutropenia occurred in 3% and severe or life-threatening neutropenia occurred in 4% of patients receiving irinotecan. The incidence of Grade 3 or 4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (9/54 [17%]).

**Neutropenic Fever/Neutropenic Sepsis:**

Based on animal data with irinotecan HCl and ONIVYDE®, neutropenic fever/neutropenic sepsis may occur in up to 10% of patients receiving ONIVYDE®/5-FU/LV. Neutropenic fever/neutropenic sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV.

**Gastrointestinal Disorders:**

The most common, severe gastrointestinal reactions requiring dose reductions were diarrhea and vomiting. The most common, severe gastrointestinal reactions requiring dose reductions were diarrhea and vomiting. Diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV.

**Infestations and Infections:**

Infections and infestations were the most common adverse reaction, occurring in 38% of patients receiving ONIVYDE®. Sepsis occurred in 4% of patients receiving ONIVYDE®. Neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®. The incidence of Grade 3 or 4 neutropenic fever/neutropenic sepsis was 1% in patients receiving ONIVYDE®.

**Metabolism and Nutrition Disorders:**

The most common, severe adverse reactions were neutropenia, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions were neutropenia, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions were neutropenia, vomiting, and sepsis.

**Skin and Subcutaneous Tissue Disorders:**

The most common, severe skin and subcutaneous tissue disorder was rash, occurring in 8% of patients receiving ONIVYDE®. Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration, were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.

**7 DRUG INTERACTIONS**

**7.1 Strong CYP3A4 Inducers:** Following administration of non-liposomal irinotecan (ie, irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John’s wort) if possible. Substituting other enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

**7.2 Strong CYP3A4 or UGT1A1 Inhibitors:** Following administration of non-liposomal irinotecan (ie, irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE® with other inhibitors of CYP3A4 (eg, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (eg, atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors ≥1 week prior to starting ONIVYDE® therapy (see Clinical Pharmacology, 12.3).

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy, Risk Summary:** Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology, 12.1). There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis (see Data in the full Prescribing Information). Advise pregnant women of the potential risk to a fetus.

**8.2 Lactation, Risk Summary:** There is no information regarding the presence of irinotecan or irinotecan metabolites in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk (see Data in the full Prescribing Information).

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE®, advise a nursing woman not to breastfeed during treatment with ONIVYDE® and for 1 month after the final dose.

**8.3 Females and Males of Reproductive Potential, Contraception, Females:** ONIVYDE® can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations, 8.1). Advise females of reproductive potential to use effective contraceptive methods during treatment with ONIVYDE® and for 1 month after the final dose. Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE® and for 4 months after the final dose (see Nonclinical Toxicology, 13.1).

**8.4 Pediatric Use:** Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

**8.5 Geriatric Use:** Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/5-FU/LV in Study 1, 49% were 65 years old and 13% were ≥75 years old. Most of these were received by patients and younger patients.

**10 OVERDOSAGE**

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥5% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/5-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. **Hematology:** anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). **Metabolic:** increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). **Renal:** increased creatinine (any 18%, 13%; severe 0%, 0%).
Frontline Treatment Strategies Propel Immunotherapy Forward in Advanced NSCLC

by HAYLEY VIRGIL

IMMUNOTHERAPY AGENTS HAVE OPENED up the treatment landscape for patients with metastatic non–small cell lung cancer (NSCLC). Despite efficacy seen in the frontline setting, second-line treatment strategies are not clear for patients who have progressive disease, according to Julie R. Brahmer, MD, MSc, FASCO.

“For patients with metastatic NSCLC, therapy options are wide and varied, but immunotherapy is now the mainstay of first-line treatment for cancers without a TKI [tyrosine kinase inhibitor]-treatable driver mutation,” said Brahmer, codirector of the Upper Aerodigestive Department at Bloomberg~Kimmel Institute for Cancer Immunotherapy and a professor of oncology at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

“[Patients with] immunotherapy refractory disease [represent] a huge unmet need, with multiple clinical trials ongoing to improve this,” Brahmer said.

During the 5th Annual International Congress on Immunotherapies in Cancer (ICIC 2020), Brahmer discussed the use of immunotherapeutics as both single agents and in combination with other agents. Additionally, Brahmer discussed the rationale for moving this drug class into the resectable, early-stage setting and the ongoing studies that may support their use in this patient population.

SINGLE-AGENT FIRST-LINE IMMUNOTHERAPIES

The first-line treatment paradigm for patients with advanced NSCLC is built around PD-L1 expression in both the tumor and/or immune cells, with several agents approved for indications stratified by expression. In particular, pembrolizumab (Keytruda) and atezolizumab (Tecentriq) stand out as the single-agent therapies of choice based on efficacy in patients with PD-L1-positive disease.

“PD-L1 level is associated with increased response rate and improved survival in patients treated with a checkpoint blockade,” Brahmer said. “We know that the higher the PD-L1 [expression], the higher the chance of a response, as noted in the original KEYNOTE-001 study [NCT01295827].”

For pembrolizumab specifically, data from KEYNOTE-001 showed that treatment-naïve patients with a tumor proportion score (TPS) of at least 50% had an overall response rate of 50.0% compared with 19.2% in patients with a TPS of 1% to 49%, and 16.7% in those with a TPS less than 1%.

Additionally, updated data from the KEYNOTE-042 trial (NCT02220894) showed that patients with previously untreated advanced NSCLC with a PD-L1 expression of at least 50% yielded longer overall survival (OS) when receiving pembrolizumab compared with chemotherapy (30.0 vs 14.2 months; HR, 0.63; 95% CI, 0.47-0.86).

In addition to pembrolizumab, single-agent atezolizumab (Tecentriq) received approval for the treatment of patients with metastatic PD-L1-high disease, defined as at least 50% of tumor cells PD-L1 stained, or PD-L1-stained tumor-infiltrating immune cells covering at least 10% of the tumor area (TABLE). The approval was based on data from IMpower110 (NCT02409342), in which atezolizumab demonstrated a median OS of 20.2 months (95% CI, 16.5-Not evaluable) at a median follow-up of 15.7 months compared with 13.1 months (95% CI, 7.4-16.5) in patients treated with platinum-based chemotherapy (HR, 0.59; 95% CI, 0.40-0.89; P = .0106).
FRONTLINE COMBINATION IMMUNOTHERAPY REGIMENS

Patient response rates can be increased by combining immunotherapy agents with other treatments, such as chemotherapy. The space has seen a number of FDA-approved agents within the past few years, primarily in patients without EGFR or ALK alterations.

“A nice [development] in these chemotherapy/immunotherapy combinations is PD-L1-agnostic agents, where a survival benefit is seen across all patient subgroups,” Brahmer said.

KEYNOTE-189 (NCT02578680) exemplified the benefit provided by an immunotherapy/chemotherapy combination in patients with previously untreated, metastatic nonsquamous NSCLC. The trial evaluated pembrolizumab or placebo plus pemetrexed and platinum chemotherapy. In final analysis data, the median OS was 22.0 months (95% CI, 19.5-24.5) in the chemotherapy arm compared with 10.6 months (95% CI, 8.7-13.6) in the placebo arm (HR, 0.56; 95% CI, 0.46-0.69). The 24-month OS rates were 45.7% and 27.9%, respectively.

“If you look across the different PD-L1 subtypes, there is improvement in survival regardless of PD-L1 expression,” Brahmer noted.

Further, in KEYNOTE-407 (NCT02775435) pembrolizumab plus chemotherapy improved overall response rates compared with placebo and chemotherapy (57.9% vs 38.4%, respectively). Patients across all PD-L1 subgroups had improved response rates with the addition of pembrolizumab, as well: 63.2% vs 40.4% in PD-L1-negative patients (TPS, < 1%), 49.5% vs 41.3% for a TPS of 1% to 49%, and 60.3% vs 32.9% for a TPS of at least 50%.

In addition to its role as a single agent, atezolizumab also demonstrated efficacy in combination with carboplatin and nab-paclitaxel (Abraxane) in patients with nonsquamous disease in IMpower130 (NCT02367781). Findings showed that the immunotherapy/chemotherapy regimen significantly improved OS in the intention-to-treat wild-type population. Patients who received the atezolizumab had a median OS of 18.6 months (95% CI, 16.0-21.2) compared with 13.9 months (95% CI, 12.0-18.7) for those who received chemotherapy alone (HR, 0.79; 95% CI, 0.64-0.98; P = .033).

Although there are a handful of biomarkers available to inform treatment with immunotherapy, such as PD-L1 expression, their use does not strictly guide treatment decisions with combination regimens.

“For chemotherapy in combination with a PD-1 antibody, the PD-L1 or tumor mutational burden biomarkers cancel out in this setting,” Brahmer explained. “Improvement in OS is seen across most subsets.”

There is an unmet need regarding treatments for patients who progress on a single agent or combination immunotherapy regimen. “This is where clinical trials, at least in a lot of our practice, fill that void,” Brahmer said. However, she added that response rates at present are approximately 10% to 20% for patients with refractory disease. “We have a lot of work to do in this space.”

THE FUTURE OF IMMUNOTHERAPEUTICS IN RESECTABLE EARLY-STAGE DISEASE

Neoadjuvant PD-1 and PD-L1 agents have been shown to be safe and feasible in patients with resectable NSCLC, demonstrating promising major pathologic response (mPR) rates in this population. This includes data from the NADIM trial (NCT03081689), which assessed the efficacy of neoadjuvant chemotherapy and nivolumab (Opdivo) in patients with stage IIIA local NSCLC, determined as surgically resectable.

Participants received 3 cycles of nivolumab plus paclitaxel and carboplatin followed by surgery and adjuvant nivolumab for 1 year. Of 46 patients enrolled in the intention-to-treat population, 41 underwent surgery and all tumors were deemed resectable. Thirty-three patients (72%) had a partial response and 3 patients (6.5%) had a complete response by RECIST criteria. Thirty-five (85%) achieved major pathologic response (95% CI, 71%-95%), including 25 (71.4%) with a complete pathologic response (95% CI, 54%-87%). Downstaging was seen in 90% (95% CI, 81%-100%) of patients.

Additionally, CheckMate 816 (NCT02998528) is comparing the use of neoadjuvant nivolumab and ipilimumab (Yervoy) or nivolumab plus chemotherapy versus chemotherapy alone to determine the safety and efficacy of each regimen for patients with early-stage NSCLC.

“Immunotherapy does hold the promise to help increase the chance of cure in resectable early-stage disease, but we have to wait for the results of the clinical trials that are…ongoing,” Brahmer concluded.

For a full list of references, see the article at https://bit.ly/35mSSGC.

TABLE. Approval Snapshot: Atezolizumab

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Atezolizumab (n = 107)</th>
<th>Platinum-based chemotherapy (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>20.2 (16.5-NE)</td>
<td>13.1 (7.4-16.5)</td>
</tr>
<tr>
<td>HR</td>
<td>0.59 (95% CI, 0.40-0.89; P = .0106)</td>
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<tr>
<td>Deaths</td>
<td>4%</td>
<td>58%</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.1 (6.8-11.0)</td>
<td>5.0 (4.2-5.7)</td>
</tr>
<tr>
<td>HR</td>
<td>0.63 (95% CI, 0.45-0.88)</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)*</td>
<td>38% (29%-48%)</td>
<td>29% (20%-39%)</td>
</tr>
</tbody>
</table>

Adverse events

The most common adverse events (≥ 20%) with single-agent atezolizumab were fatigue/asthenia, nausea, cough, dyspnea, and decreased appetite.

*Investigator-assessed data.

NE, not evaluable; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
In the frontline setting, cisplatin has demonstrated improved survival rates with some curative benefit; however, up to two-thirds of patients with mBC are cisplatin-ineligible because of comorbidities and therefore are not able to derive benefit and generally have poor outcomes.

The decisions were based on findings from cohort 1 of the phase 2 IMvigor210 trial (NCT02108652) and the phase 2 KEYNOTE-052 (NCT02335424) trials, respectively. The objective response rate (ORR) was 23.5% with atezolizumab (n = 119) and 28.6% with pembrolizumab (n = 370).1

However, in May 2018, the FDA issued a safety alert of decreased survival associated with single-agent atezolizumab or pembrolizumab among patients with mBC who have not received prior therapy and who have low PD-L1 expression based on findings from the confirmatory phase 3 IMvigor130 (NCT02807636) and KEYNOTE-361 (NCT02853305) trials.2,3 As such, updates to the agents’ labels require the use of an FDA-approved companion diagnostic to determine PD-L1 expression for patients with advanced cisplatin-ineligible bladder cancer.4

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“Systematically, we had to roll back some of the excitement [generated with first-line checkpoint inhibitors] when the label was restricted to those who are PD-L1-positive or chemotherapy ineligible. Now there is some controversy about [checkpoint inhibitors’] continued use at all in the first-line setting,” Balar said.

Specifically, subgroup analyses of overall survival (OS) showed that patients with PD-L1-negative disease have an increased risk of death within the first year with single-agent atezolizumab compared with chemotherapy, which led to the FDA label change.

Balar pointed to updated findings from the IMvigor130 trial, in which the progression-free survival (PFS) in the intention-to-treat population was 8.2 months (95% CI, 6.5-8.3) with atezolizumab plus chemotherapy versus 6.3 months (95% CI, 6.2-7.0) with placebo plus chemotherapy (stratified HR, 0.82; 95% CI, 0.70-0.96; one-sided P = .007), meeting the coprimary end point of the study.2

“Anytime we look at a curve like this, we think, yes, it is statistically significant, but is it clinically meaningful?” Balar said. “The curves separate, and they maintain separation, but in terms of what we were hoping to see, it certainly didn’t mirror what we saw in advanced lung cancer.”

The KEYNOTE-361 trial yielded similar findings, although the PFS results did not meet statistical significance.3

Results of the phase 3 JAVELIN Bladder 100 trial (NCT02603432) carved out a role for chemotherapy in combination with immunotherapy, although Balar noted this was a maintenance therapy–powered trial. Investigators observed a 31% reduction in the risk of death with avelumab (Bavencio) maintenance versus best supportive care (BSC) in the overall population of patients with unresectable locally advanced or mBC who derived a complete or partial response or stable disease with standard first-line chemotherapy (95% CI, 0.56-0.86; P < .001).5 In the PD-L1-positive population, the risk of death was reduced by 44% (95% CI, 0.40-0.79; P < .001).

Notably, 6.3% of patients who received avelumab plus BSC (n = 350) and 43.7% of patients who received BSC alone (n = 350) discontinued maintenance therapy and received a PD-1/PD-L1 inhibitor as subsequent therapy. In June 2020, the FDA approved avelumab for the maintenance treatment of patients with locally advanced or mBC that has not progressed with first-line platinum-containing chemotherapy.6

CONTINUED ON PAGE 49
IN THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (Pd)

ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS

SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010). SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1
CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; NCCN=National Comprehensive Cancer Network; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)2

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

Indication
SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Important Safety Information
CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS
Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Choose SARCLISA + Pd to Offer Improved Outcomes to More Patients vs Pd Alone

Based on the ICARIA-MM trial, SARCLISA + Pd is a treatment choice for patients with relapsed refractory multiple myeloma

- Who have received at least 2 prior therapies, including lenalidomide and a PI
- Who may have renal impairment (creatinine clearance <60 mL/min/1.73 m²), high cytogenetic risk, or a history of COPD or asthma
- Who may have poor performance status or are ≥75 years of age
- Who are refractory to lenalidomide, a PI, or both

STUDY DESIGN: ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint; ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.1

PATIENT CHARACTERISTICS: The median patient age was 67 years (range, 36 to 86), and 20% of patients were ≥75 years of age. Ten percent of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The ISS stage at study entry was I in 37%, II in 36%, and III in 25% of patients. Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14), and t(14;16) were present in 12%, 8%, and 2% of patients, respectively. The median number of prior lines of therapy was 3 (range, 2 to 11). All patients received a prior PI, all patients received prior lenalidomide, and 56% of patients received prior stem cell transplantation; the majority of patients (93%) were refractory to lenalidomide, 76% to a PI, and 73% to both an immunomodulator and a PI.1

COPD=chronic obstructive pulmonary disease; ISS=International Staging System; IV=intravenous; OS=overall survival; PI=proteasome inhibitor.

Important Safety Information (cont’d)

Infusion-Related Reactions (cont’d)

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.
SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd. At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.  

SARCLISA + Pd showed a significant increase in ORR

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
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<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td><strong>31.8%</strong> ≥VGPR</td>
<td><strong>8.5%</strong> ≥VGPR</td>
</tr>
<tr>
<td>35 days</td>
<td>Median time to first response among responders 58 days</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

**Important Safety Information (cont’d)**

**Neutropenia**
SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Important Safety Information (cont’d)

Neutropenia (cont’d)
Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA–multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA–treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol–treated RBCs. If an emergency transfusion is required, non–cross–matched ABO/RhD–compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M–protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality, 96% Isa-Pd vs 92% Pd), infusion–related reactions (38% Isa–Pd vs 0% Pd), pneumonia (31% Isa–Pd vs 23% Pd), upper respiratory tract infection (57% Isa–Pd vs 42% Pd), and diarrhea (26% with Isa–Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in >5% of patients who received Isa–Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab–irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.

SARCLISA® Rx Only (isatuximab-irfc) injection, for intravenous use
Brief Summary of Prescribing Information

1. Indications and Dosage
SARCLISA is indicated, in combination with pomalidomide and dexamethasome, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

2. DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
Administer pre-infusion medications (see Dosage and Administration (2.2-2.3))

2.2 Recommended Premedications
Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions (see Warnings and Precautions (5.1)):
- Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age).
- Acetaminophen 650 mg to 1000 mg orally (or equivalent).
- H2 antagonists.
- Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

2.3 Dose Modifications
No dose reduction of SARCLISA is recommended. Dose delay may be considered if the patient is unable to receive the recommended dose due to hematological toxicity (see Warnings and Precautions (5.2, 5.4)). For information concerning drugs given in combination with SARCLISA, see manufacturer’s prescribing information. For other medical products that are administered with SARCLISA, refer to the respective current prescribing information.

2.4 Preparation
Prepare the solution for infusion using aseptic technique as follows:
- Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) (see Dosage and Administration (2.1)). More than one SARCLISA vial may be necessary to obtain the required dose for the patient.
- Parenteral drug products should be inspected visually for particulate matter and discontinue administration, whenever such matter is present or container broken.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration
- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadine [PBD], or polyurethane [PU] with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will fill the infusion bag (see Table 1).
- Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–8°C, followed by 8 hours (including the infusion time) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

Infusion Rates
Following infusion, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 1. Incremental escalation of the infusion rate should be considered only when infusion-related reactions are noted (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

Table 1: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Days</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>1, 8, 15, and 22 (weekly)</td>
<td></td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>1, 2, 15 (every 2 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Initial Rate</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL/h</td>
<td>50 mL/h every 30 minutes</td>
<td>200 mL/h</td>
</tr>
</tbody>
</table>

4 CONTRAINdications
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients (see Warnings and Precautions (5.1)).

5.1 Warnings and Precautions
5.1.1 Infusion-related Reactions
Infusion-related reactions have been observed in 38% of patients treated with SARCLISA (see Adverse Reactions (6.1)). All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 98% of cases. The majority of infusion-related reactions were mild to moderate (grade 1 or 2). In the majority of cases, the symptoms resolved without interrupting the infusion.

5.2 Neutropenia
SARCLISA may cause neutropenia. Neutropenia (reported in 0.7% of patients in the Isa-Pd arm, breast angiosarcoma (0.7% in the Isa-Pd arm and in 0.7% of patients in the Isa-Pd arm), breast angiosarcoma (0.7% in the Isa-Pd arm) and myelodysplastic syndrome

5.3 Second Primary Malignancies
Second primary malignancies were reported in 3% of patients in the Isa-Pd arm and in 0.7% of patients in the pomalidomide and dexamethasome (PaD) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome

5.4 Laboratory Test Interference
Immunofixation Tests
Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of monoclonal IgG protein. This interference may impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein [see Drug Interactions (7.1)].

5.5 Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal harm when administered to pregnant women (see Animal Data (5.6)).

6. ADVERSE REACTIONS
The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:
- Infusion-related Reactions (see Warnings and Precautions (5.1))
- Neutropenia (see Warnings and Precautions (5.2))
- Second Primary Malignancies (see Warnings and Precautions (5.3))

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

6.2 Multicenter Myeloma
The safety of SARCLISA was evaluated in ICARA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm³, absolute neutrophil count ≥1.5 × 10⁹ cells/mm³, creatinine clearance ≥30 mL/min (MDRD formula), and AST and/or ALT ≤3 × ULN. Patients receiving SARCLISA 10 mg/kg intravenously, who were exposed to SARCLISA for 6 months or longer, second primary malignancies were reported in 3% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% were pneumonia and other infections [3%]).

Permanent discontinuation due to an adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (7%). SARCLISA was discontinued in 3% of patients due to infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reactions requiring a dose delay interruption were infusion-related reaction (28%).
The most common adverse reactions (>20%) were neuropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea.

Table 3 summarizes the adverse reactions in ICARIA-MM.

### Table 3: Adverse Reactions (>10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (n=142)</th>
<th>Pomalidomide + Dexamethasone (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>Grade 1: 38 (27%), Grade 2: 13 (9%)</td>
<td>Grade 1: 0 (0%), Grade 2: 0 (0%)</td>
</tr>
<tr>
<td>Infections</td>
<td><em>Pneumonia</em> 31 (22%)</td>
<td>32 (21%)</td>
</tr>
<tr>
<td></td>
<td><em>Upper respiratory tract infection</em> 57 (40%)</td>
<td>45 (30%)</td>
</tr>
<tr>
<td></td>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Fetal/neonatal</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Dyspnea</em> 17 (12%)</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Diarrhea</em> 26 (18%)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td></td>
<td><em>Nausea</em> 15 (10%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td></td>
<td><em>Vomiting</em> 12 (8%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td></td>
<td><em>Other</em></td>
<td>12 (8%)</td>
</tr>
</tbody>
</table>

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*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jiroveci pneumonia.*

Upper respiratory tract infection includes bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, macrophage activation syndrome, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial. Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the laboratory abnormalities in ICARIA-MM.

### Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment — ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (n=112)</th>
<th>Pomalidomide + Dexamethasone (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Grade 3: 4 (4%)</td>
<td>Grade 4: 5 (5%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3: 12 (11%)</td>
<td>Grade 4: 19 (16%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Grade 3: 14 (13%)</td>
<td>Grade 4: 23 (20%)</td>
</tr>
<tr>
<td>Hemoglobinopenia</td>
<td>Grade 3: 14 (13%)</td>
<td>Grade 4: 19 (16%)</td>
</tr>
</tbody>
</table>

Description of Selected Adverse Reactions

Infusion-related reactions in ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISIA infusion), with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (39%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 55 minutes.

In a separate study (T074979 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 45% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

### 6.2 Immunogenicity

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

In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ADAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

### 7 Drug Interactions

#### 7.1 Laboratory Test Interference

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA (see Warnings and Precautions (5.4)).

Interference with Serum Protein Electrophoresis and Immunofixation tests

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see Warnings and Precautions (5.4)).

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on SARCLISA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects, miscarriage, or other adverse outcomes is based on data from clinical trials with SARCLISA (see Warnings and Precautions (5.4)).

**Interruption**

Refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

**Males**

Refer to the pomalidomide prescribing information.

#### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

#### 8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (308 patients) were 65 or over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years of age and older patients, but greater sensitivity of some older individuals cannot be ruled out.

### 10 OVERDOSAGE

There is no known specific antidote for SARCLISA overdose. In the event of overdose of SARCLISA, refer to the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

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SARCLISA® (isatuximab-irfc) injection, for intravenous use

**Data**

Animal data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetomaternal immune tolerance (mice), and early embryonic development (frogs).

**2.8 Lactation**

**Risk Summary**

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

**8.3 Females and Males of Reproductive Potential**

**Pregnancy Testing**

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

**Contraception**

Females

SARCLISA can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations (8.1)). Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

**Males**

Refer to the pomalidomide prescribing information.

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Safety and effectiveness in pediatric patients have not been established.

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Of the total number of subjects in clinical studies of SARCLISA, 53% (308 patients) were 65 and over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years of age and older patients, but greater sensitivity of some older individuals cannot be ruled out.

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“This, plus some of the data from [KEYNOTE-361], is saying that maybe we should give everyone platinum-based chemotherapy up front and really reserve immunotherapy for the second-line setting,” Balar said.

“High-volume, symptomatic disease has to be treated with chemotherapy, in my opinion, irrespective of PD-L1 status,” he added. “Small-volume, asymptomatic disease can be treated effectively with immunotherapy, also irrespective of PD-L1 status. PD-L1 expression is a dubious value in metastatic disease. Perhaps, [PD-L1 status is useful] in equivocal cases where we are not sure what direction to go in. For chemotherapy-ineligible patients, immunotherapy remains the only viable option.”

Other ongoing trials are continuing to parse out the role of immunotherapy, particularly by evaluating CTLA-4 inhibitors in the metastatic setting. However, the phase 3 DANUBE trial (NCT02516241), which evaluated durvalumab (Imfinzi) with or without tremelimumab versus chemotherapy alone, did not meet either of its coprimary end points.2

EMERGING OPTIONS IN THE METASTATIC SPACE

Antibody-drug conjugates, such as enfortumab vedotin-ejfv (Padcev) and sacituzumab govestac-hziy (Trodelvy), could potentially reshape the third-line treatment of patients with mBC, Balar said.

In December 2019, enfortumab vedotin received an accelerated approval from the FDA for the treatment of patients with locally advanced or mBC after prior PD-L1/ PD-L1 therapy and platinum-containing chemotherapy. Long-term follow-up of the EV-201 trial, findings of which served as the basis for the approval, demonstrated a 50.4% OS rate at 12 months and a 34.2% OS rate at 18 months with enfortumab vedotin in this patient population.8

Additionally, combinations with ADCs and checkpoint inhibitors, such as enfortumab vedotin and pembrolizumab in the ongoing phase 2 EV-103 trial (NCT03288545), are under investigation to potentially introduce chemotherapy-free options for patients with advanced disease.

MAKING WAY FOR IMMUNOTHERAPY IN MIBC/NON-MIBC

Traditionally, patients with MIBC are treated with radical cystectomy; however, a significant portion of patients relapse after surgery. Notably, single-agent immunotherapy has demonstrated pathological complete response rates in the range of 30% to 40% in the neoadjuvant setting. Additionally, checkpoint inhibitors have shown some responses in the adjuvant setting, Balar explained.

Trimodality chemoradiation plus immunotherapy is being evaluated for this patient population in the ongoing KEYNOTE-992 (NCT04241185) and SWOG 1806 trials (NCT03775265) and could offer a potential option for patients who want to avoid radical cystectomy.

Finally, initial findings from the ongoing KEYNOTE-057 trial (NCT03711032) demonstrated encouraging early efficacy and complete response rates with seemingly durable responses with pembrolizumab monotherapy in patients with high-risk non-MIBC who are unresponsive to Bacillus Calmette-Guerin and who decline to undergo or are ineligible for cystectomy, according to Balar, lead author of the study.

“The benefit of immunotherapy is still evolving, especially in the case of bladder preservation in non-muscle invasive disease and also, in particular, when we combine it with trimodality bladder preservation,” Balar concluded.

REFERENCES


Upfront Immunotherapy Continues to Show Efficacy in SCLC

by CAROLINE SEYMOUR

CHECKPOINT INHIBITORS HAVE FAILED to improve progression-free survival (PFS) and overall survival (OS) as second-line therapy and maintenance therapy for patients with small cell lung cancer (SCLC). However, this class of agents continues to show encouraging activity worthy of a paradigm shift up front.

“SCLC has been a difficult cancer to treat, and immunotherapy has not made an impact until very recently, where, in the first-line setting, we have improved outcomes and new standards of care for the treatment of SCLC,” said Naiyer A. Rizvi, MD, in a presentation during the 5th Annual International Congress on Immunotherapies in Cancer*.

The first robust trial to produce data demonstrating the potential for immunotherapy up front was the IMpower133 trial (NCT02763579). In the phase 3 trial, patients with extensive-stage SCLC were randomized 1:1 to 1200 mg of intravenous atezolizumab (Tecentriq) plus carboplatin or etoposide for four 21-day cycles, or placebo plus carboplatin or etoposide followed by maintenance atezolizumab and placebo, respectively.

The findings led to the FDA approval of atezolizumab plus chemotherapy as first-line treatment in this setting in March 2019. At a median follow-up of 13.9 months, the median PFS was 5.2 months in the atezolizumab arm versus 4.3 months in the placebo arm (HR, 0.77; 95% CI, 0.62-0.96; \(P=0.017\)). The 6-month PFS rate was 30.9% in the atezolizumab arm compared with 22.4% in the placebo arm. The 12-month PFS rates were 12.6% and 5.4%, respectively.

At a median follow-up of 22.9 months, the median OS was 12.3 months with atezolizumab versus 10.3 months with placebo (HR, 0.76; 95% CI, 0.60-0.95; \(P=.0154\)). The 18-month OS rates were 34.0% and 21.0%, respectively. The 24-month OS rates were 22.0% and 16.8%, respectively.

The median duration of response (DOR) was 4.2 months in the atezolizumab arm versus 3.9 months in the placebo arm (HR, 0.70; 95% CI, 0.53-0.92). More patients in the atezolizumab arm had an ongoing response at last follow-up compared with those in the placebo arm (18 vs 7, respectively).

In the subgroup analysis, all patients except those with brain metastases (HR, 1.07; 95% CI, 0.47-2.43) derived benefit from atezolizumab.

“IMpower133 is really the first study in over 20 years to show a meaningful improvement in OS versus standard of care in first-line SCLC. These data led to the adoption of chemotherapy plus immunotherapy as a first-line standard of care for extensive-stage SCLC,” said Rizvi, who is the Price Family Professor of Medicine, director of thoracic oncology, and codirector of cancer immunotherapy at Columbia University Herbert Irving Comprehensive Cancer Center.

The data were recapitulated in findings from the phase 3 CASPIAN trial (NCT03043872), said Rizvi. In the trial, patients with extensive-stage SCLC were randomized 1:1:1 to 1500 mg of durvalumab (Imfinzi) plus etoposide every 3 weeks for up to 4 cycles, etoposide every 3 weeks for up to 6 cycles, or durvalumab plus 75 mg of tremelimumab plus etoposide for up to 4 cycles. This was followed by durvalumab, optional prophylactic irradiation, and durvalumab, respectively.

Initial findings led to the approval of durvalumab plus chemotherapy as first-line therapy in this setting in March 2020. At over 2 years of follow-up, the median OS was 12.9 months in the durvalumab/etoposide arm versus 10.5 months in the etoposide arm (HR, 0.75; 95% CI, 0.62-0.91; \(P=.0032\)). The 24-month OS rates were 22.2% and 14.4%, respectively.

The median PFS was 5.1 months in the durvalumab/etoposide arm versus 4.3 months in the placebo arm (HR, 0.80; 95% CI, 0.66-0.96). The 12-month PFS rates were 11.0% and 2.9%, respectively.

*The trial was not powered to compare durvalumab plus chemotherapy versus durvalumab plus tremelimumab plus chemotherapy, but these 2 arms did perform fairly similarly, and both performed similarly to chemotherapy alone,” said Rizvi.

In an exploratory analysis, tumor mutational burden was not shown to be predictive of an improvement in OS for either durvalumab arm, indicating that the marker should not be used to select patients for treatment.

Despite the progress that has been made, there is room for improvement, said Rizvi, who cited the phase 3 SKYSCRAPER-02 trial (NCT04256421) as 1 study that could push the needle further. Previously untreated patients will be randomized 1:1 to 1200 mg of atezolizumab plus chemotherapy plus 600 mg of tiragolumab every 3 weeks for 4 cycles, or atezolizumab plus placebo in the same schedule, followed by atezolizumab/tiragolumab or atezolizumab/placebo, respectively.

TRYING TO CRACK THE SECOND LINE

Meanwhile, carving out a space in the second line for immunotherapeutic agents in SCLC continues to present a challenge.

Nivolumab (Opdivo) was granted accelerated approval in 2018 based on data from the phase 1/2 CheckMate 032 trial (NCT01928394) for patients with SCLC who have experienced disease progression after a platinum-based chemotherapy and at least 1 other line of therapy. Findings showed the agent elicited an objective response rate of 12% (95% CI, 6.5%-19.5%), comprised of an 11% partial response rate and a 0.9% complete response rate. The median DOR with the immunotherapy was 17.9 months (95% CI, 7.9-42.1), with more than half of the 109 patients (62%) experiencing a continued response at 12 months.

However, data from subsequent confirmatory studies in different treatment settings, including that from CheckMate 451 (NCT02538666) and CheckMate 331 (NCT02481830), did not meet their primary end points of OS. In December 2020, Bristol Myers Squibb, the developer of nivolumab, withdrew the indication for the agent.

For a full list of references, see the article at https://bit.ly/39ORE8w.
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TUNE IN!
In our exclusive interview, Dr Choueiri provides perspective on the FDA approval of nivolumab and cabozantinib in advanced renal cell carcinoma.

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Seribantumab May Hold Pan-Tumor Potential in Cancers With NRG1 Fusions

by DEISE MYSHKO

INVESTIGATORS ARE SEEKING TO determine whether seribantumab, a novel monoclonal antibody, can effectively treat patients with solid tumors that harbor rare NRG1 fusions. They are assessing the therapy in the phase 2 CRESTONE study (NCT04383210) in 15 tumor types with the molecular aberration.1

Although the biological and clinical implications of NRG1 fusions remain under study, clinical findings suggest that patients with these alterations do not respond well to standard therapies. They also have poorer disease-free and overall survival outcomes, according to investigators in a poster presented at the 2021 Gastrointestinal Cancers Symposium.2

Research findings suggest that oncogenic activity associated with NRG1 fusions is driven by HER3 overactivation. Seribantumab blocks HER3 signaling and its downstream effects.2

“Seribantumab essentially binds HER3 and inhibits both NRG1-dependent activation as well as HER2 dimerization, effectively shutting down intracellular growth-promoting PI3K and MAPK pathways,” Sam Klempner, MD, an investigator on the CRESTONE study, said in an interview with OncologyLive®. He is an assistant professor at Harvard Medical School and Massachusetts General Hospital, both in Boston. “NRG1 fusions that retain the EGF-like domain are activating oncogenic events, and they result in HER2, HER3, and HER4 activation,” Klempner explained. “This drives intracellular signaling through PI3K and MAP kinase pathways, which result in activation of cellular programs for proliferation.” NRG1 has recently emerged as a potential pan-tumor target as a result of advancements in DNA- and RNA-based next-generation sequencing, Klempner said.

Overall, NRG1 gene fusions have been identified in approximately 0.2% of solid tumors, according to an analysis of 44,570 tumor specimens. The data indicate a diversity of fusion partners and a range of incidence in tumor types. Of the specimens analyzed, NRG1 fusions were found in 54% of non–small cell lung cancers (NSCLCs), 11% of breast cancers, 7% of pancreatic ductal adenocarcinoma (PDAC) and ovarian samples, 6% of cholangiocarcinomas, and 5% of colorectal and genitourinary cancers.3

CRESTONE STUDY DETAILS

CRESTONE investigators are aiming to recruit 75 adult patients with recurrent, locally advanced, or metastatic solid tumors that have progressed or have been nonresponsive to available therapies. (FIGURE 1). Tumor types to be studied include cancers of the pancreas, lung, head and neck, breast, kidney, bladder, gall-bladder, bile duct, and prostate; colorectal, ovarian, esophageal, and uterine cancers; and sarcomas and cholangiocarcinoma.

Participants will be assigned to 1 of 3 parallel cohorts based on prior treatment status. The pivotal cohort will enroll 55 patients with advanced solid tumors with NRG1 gene fusions who have not been previously treated with pan-ERBB-

FIGURE. Seribantumab in NRG1 Fusion–Positive Solid Tumors1,2 Phase 2 CRESTONE Study

Eligibility criteria

- Locally advanced or metastatic solid tumor with an NRG1 gene fusion
- Minimum of 1 prior standard therapy
- Progressed on or lack of response to prior therapy
- ECOG performance status of 0 to 2
- At least 1 measurable extracranial lesion defined by RECIST v1.1
- Adequate hepatic functiona and hematologic statusb
- Adequate hematologic status

N = 75

Cohort 1

n = 55
No prior pan-ERBB, HER2, or HER3 targeted therapy

Cohort 2

n = 10
Prior pan-ERBB, HER2, or HER3 targeted therapy

Cohort 3

n = 10
NRG1 fusions without EGF-like domain or insufficient tissue for central testing

Therapy

Seribantumab 1-hour IV infusion at various doses once weekly, every 2 weeks, and every 3 weeks, during the induction, consolidation, and maintenance dosing phases, respectively.

End points

Primary
- ORR
- CBR
- PFS
- OS
- Safety

Secondary
- DOR
- ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; CBR, clinical benefit rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ULN, upper limit normal.

aDefined as serum AST and ALT < 2.5 x ULN or AST and ALT < 5 x ULN; total bilirubin < 2.0 x ULN.
bDefined as ANC ≥ 1.5 x 10⁹/L and platelet count ≥ 150.0 x 10⁹/L with no transfusion support for at least 7 days prior to screening.
HER2-, or HER3- directed therapy. The second cohort will enroll 10 patients with NRG1 gene fusions whose prior treatment included those targeted therapies. The third cohort will enroll 10 participants with NRG1 fusions that lack an EGF-like domain or who have insufficient tissue for central confirmatory testing.

In all cohorts, the investigators will administer seribatumab in various doses via 1-hour intravenous infusion once weekly, every 2 weeks, and every 3 weeks. Administration will take place during the induction, consolidation, and maintenance dosing phases, respectively.

The primary end point is the objective response rate according to RECIST 1.1 criteria by independent radiologic review. Investigators will conduct an interim analysis after 20 patients with a centrally confirmed NRG1 fusion are enrolled in cohort 1, potentially in mid-2021, according to Elevation Oncology, the company developing seribatumab.

Secondary end points include duration of response, safety, progression-free survival, overall survival, and clinical benefit rate. Exploratory investigations will include the clinical relevance of NRG1 fusion partners, impact of prior therapies, and resistance mechanisms.

The preferred method for determining a patient’s NRG1 fusion status for study participation is RNA-based sequencing, according to Klempner; a centrally confirmed result will be needed for assignment to cohort 1. “The NRG1 gene is quite large, and DNA-based platforms may have slightly lower sensitivity for fusion detection,” he said.

Nevertheless, investigators will consider for the other cohorts patients who are identified in local settings with molecular assays approved under Clinical Laboratory Improvement Amendments standards.

FAVORABLE SERIBANTUMAB SIGNALS

The scientific rationale for the CRESTONE study is supported by results from case reports and preclinical data, investigators said in their conference poster. Notably, they highlighted the therapeutic potential of targeting NRG1 fusions in pancreatic and other gastrointestinal cancers. In PDAC, the alterations appear to be mutually exclusive with KRAS activating mutations.

The most extensive case report findings show that afatinib (Gilotrif), a pan-HER tyrosine kinase inhibitor, elicited partial responses or stable disease in 6 patients with NRG1 fusions: 3 had stage IV PDAC, 1 had cholangiocarcinoma, and 2 had colorectal cancer. One patient with KRAS wild-type PDAC with liver metastases achieved a partial response that is ongoing after more than 7 months and another patient with KRAS-mutant stage IVB colorectal cancer with liver and lung metastases maintained stable disease for 16 months.

Further, seribatumab reduced tumor volume from 50% to 100% in patient-derived xenograft models of invasive mucinous lung adenocarcinoma and high-grade serous ovarian cancer, according to findings presented at the 32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in October 2020, hosted by the European Organisation for Research and Treatment of Cancer, National Cancer Institute, and the American Association for Cancer Research. Investigators found that seribatumab was more effective than afatinib in these models.

The data demonstrate that treatment with seribatumab results in decreased phosphorylation of not only HER3 but also its dimerization partners HER2, HER4, and EGFR, and downstream PI3K and MAPK signaling pathways, suggesting efficient inhibition across HER3 and the entire ERBB signaling pathway, lead author Igor Odintsov, MD, a research fellow at Memorial Sloan Kettering Cancer Center in New York, New York, said in a press release.

PRIOR DEVELOPMENT

CRESTONE represents another opportunity to develop seribatumab, which has been studied over the years in monotherapy and combination trials. Formerly known as MM-121, seribatumab was evaluated in the phase 2 SHERLOC (NCT02387216) study in combination with docetaxel in patients with previously treated advanced or metastatic heregulin-positive NSCLC. The study was terminated in October 2018 after investigators determined in an interim analysis that the combination did not improve progression-free survival over docetaxel alone. Less than a month later, Merrimack Pharmaceuticals, the company developing the drug at that time, halted all development of seribatumab, including its SHERBOC trial (NCT03241810) in combination with fulvestrant (Faslodex) in postmenopausal women with metastatic breast cancer.

Elevation Oncology acquired seribatumab in 2019 and repurposed the agent to target NRG1-fusion cancers. The development program is building on prior clinical experience from more than 800 patients demonstrating consistent safety and tolerability, although previous trials did not select for tumors with an NRG1 fusion.

In SHERLOC, the most common treatment-emergent adverse effects among 71 patients treated with seribatumab plus docetaxel included diarrhea (50.7%), fatigue (45.1%), nausea and decreased appetite (33.8% each), asthenia (31.0%), and neutropenia (28.2%). The most common events of grade 3 or higher severity included neutropenia (22.5%), a decrease in neutrophil count (11.3%), and pneumonia (9.9%).

For a full list of references, see the article at OncLive.com.
In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:

29% reduction in risk of PFS event*  
(HR: 0.71; 95% CI: 0.54, 0.93; P = 0.011): median PFS 48.2 vs 20.8 months  
for A+CHP and CHOP, respectively; primary endpoint  
*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.

Indication
ADCETRIS® (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

Important Safety Information

BOXED WARNING
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication
ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

Warnings and Precautions
- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesis, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
reduction in risk of death

(\text{HR} = 0.66; \text{CI}: 0.46, 0.95; \text{P} = 0.024); \text{key secondary endpoint}\textsuperscript{1,2}

\text{†Median overall survival follow-up of 42.1 months with A+CHP and CHOP; median overall survival not reached in either treatment arm.}\textsuperscript{3}

**ECHELON-2 trial design:** A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (\text{n} = 226) or CHOP (\text{n} = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator’s discretion. Primary endpoint was PFS per IRF, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.\textsuperscript{2,3}

**Most common adverse reactions (≥20%) in combination with CHP**

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.\textsuperscript{2}

A+CHP = ADCETRIS + cyclophosphamide, doxorubicin, prednisone; ALC = anaplastic large cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHP = cyclophosphamide, doxorubicin, prednisone; CI = confidence interval; HR = hazard ratio; IRF = independent review facility; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma.
Important Safety Information, cont’d

- **Anaphylaxis and infusion reactions:** Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS® (brentuximab vedotin). Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include atemizoline, an antihistamine, and a corticosteroid.

- **Hematologic toxicities:** Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma or previously untreated PTCL. Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- **Serious infections and opportunistic infections:** Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS–treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.

- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor and high tumor burden.

- **Increased toxicity in the presence of severe renal impairment:** The frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.

- **Increased toxicity in the presence of moderate or severe hepatic impairment:** The frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.

- **Hepatotoxicity:** Fatal and serious cases have occurred in ADCETRIS–treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

- **PML:** Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS–treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- **Pulmonary toxicity:** Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

- **Serious dermatologic reactions:** Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- **Gastrointestinal (GI) complications:** Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

- **Embryo-fetal toxicity:** Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

**Most Common (≥20% in any study)**

**Adverse Reactions**

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

**Drug Interactions**

Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE).

**Use in Specific Populations**

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages and full Prescribing information at [adcetrispro.com](http://adcetrispro.com)

**References:**


NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
ADCEYXIR® (bretuximab vedotin) for injection, for intravenous use

Brief Summary: see package insert for full prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
JC virus infection resulting in PML and death can occur in patients receiving ADCEYXIR.

1 INDICATIONS AND USAGE
ADCEYXIR is a CD19-directed antibody-drug conjugate indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD19-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL, not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
For dosing instructions of combination agents administered with ADCEYXIR, see the manufacturer's prescribing information.

Administer ADCEYXIR as a 30-minute intravenous infusion. The recommended dose is 1.8 mg/kg up to a maximum of 180 mg in combination with cyclophosphamide, doxorubicin, and prednisone (CHP), administered every 3 weeks with each cycle of chemotherapy for 6 to 8 doses. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [CrCl] <30 mL/min). The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

2.2 Recommended Prophylactic Medications
In patients with previously untreated PTCL who are treated with ADCEYXIR + CHP, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification
Peripheral Neutropenia: For Grade 2 motor neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 sensory neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 motor neuropathy, discontinue dose. For Grade 4 sensory or motor neuropathy, discontinue dose. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Neutropenia: For Grade 3 or 4 neutropenia, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

4 CONTRAINDICATIONS
ADCEYXIR is contraindicated with concurrent bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

5 WARNINGS AND PRECAUTIONS
5.1 Peripheral Neuropathy
ADCEYXIR treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCEYXIR-induced peripheral neuropathy is cumulative.

In ECHLON-2 (Study 6), 52% of patients treated with ADCEYXIR + CHP experienced new or worsening peripheral neuropathy of any grade (by maximum grade, 34% Grade 1, 12% Grade 2, 1% Grade 3), in patients treated predominantly sensory (84% sensory, 16% motor) and had a median onset time of 2 months (range, 1-18). At last evaluation, 50% had complete resolution of neuropathy, 12% had partial improvement, and 38% had no improvement. The median time to improvement was 4 months (range, 1-18). Of patients with residual neuropathy at last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCEYXIR.

5.2 Anaphylaxis and Infusion Reactions
Infusion-related reactions, including anaphylaxis, have occurred with ADCEYXIR. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCEYXIR and administer appropriate medical therapy. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities
Fetal and serious cases of febrile neutropenia have been reported with ADCEYXIR. Prolonged (>1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCEYXIR.

Start primary prophylaxis with G-CSF beginning with Cycle 1 for patients who receive ADCEYXIR in combination with chemotherapy for previously untreated Stage III/IV classical Hodgkin lymphoma (CHL) or previously untreated PTCL.

Monitor complete blood counts prior to each dose of ADCEYXIR. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCEYXIR doses.

5.4 Serious Infections and Opportunistic Infections
Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCEYXIR. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome
Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment
The frequency of Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MAAE exposure, severe Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCEYXIR in patients with severe renal impairment (CrCL <30 mL/min).

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment
The frequency of Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCEYXIR in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

5.8 Hepatotoxicity
Fatal and serious cases of hepatotoxicity have occurred in patients receiving ADCEYXIR. Cases were consistent with hepatoxicity injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCEYXIR or after ADCEYXIR rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCEYXIR.

5.9 Progressive Multifocal Leukoencephalopathy
Fatal cases of JC virus infection resulting in PML have been reported in ADCEYXIR-treated patients. First onset of symptoms occurred at various times from initiation of ADCEYXIR therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCEYXIR therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCEYXIR dosing for any suspected case of PML and discontinue ADCEYXIR dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity
Fatal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), have been reported, Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCEYXIR dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions
Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCEYXIR. If SJS or TEN occurs, discontinue ADCEYXIR and administer appropriate medical therapy.

5.12 Gastrointestinal Complications
Fatal and serious events of acute pancreatitis have been reported. Fatal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, colitis, and de novo lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, ADCEYXIR can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCEYXIR in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased fetal viability and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks. Advise females of reproductive potential to avoid pregnancy during ADCEYXIR treatment and for at least 6 months after the final dose of ADCEYXIR. Advise a pregnant woman of the potential risk to the fetus.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The most common adverse reactions (≥20%) in combination with CHP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

Previously Untreated sALCL or Other CD30-Expressing PTCL (Study 6, ECHELON-2)

ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30-expressing PTCL, in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADCETRIS + CHP or CHOP for 6 to 8, 21-day cycles. ADCETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHP. The trial required hepatic transaminases ≤3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy. A total of 449 patients were treated (223 with ADCETRIS + CHP, 226 with CHOP, with 6 cycles planned in 81%, in the ADCETRIS + CHP arm, 70% of patients received 6 cycles, and 18% received 8 cycles; primary prophylaxis with S-DF was administered to 34% of ADCETRIS + CHP-treated patients and 27% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the CHOP arm and 4% of patients in the ADCETRIS + CHP arm, most often from infection. Serious adverse reactions were reported in 38% of ADCETRIS + CHP-treated patients and 35% of CHOP-treated patients. Serious adverse reactions occurring in ≥3% of ADCETRIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (9%), pyrexia (4%), and sepsis (3%).

The most common adverse reactions observed in ≥2% more in recipients of ADCETRIS + CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥1%) adverse reactions observed in ≥2% more with ADCETRIS + CHP were febrile neutropenia, abdominal pain, decreased appetite, dyspnea, edema, cough, diarrhea, hypokalemia, decreased weight, and myalgia. In recipients of ADCETRIS + CHP, adverse reactions led to dose delays of ADCETRIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCETRIS with or without other components in 7% (most often from peripheral neuropathy and infection).

Table 7: Adverse Reactions Reported in ≥10% of ADCETRIS + CHP-Treated Patients with Previously Untreated, CD30-Expressing PTCL (Study 6, ECHELON-2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCETRIS + CHP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
<td>56%</td>
<td>13%</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>59%</td>
<td>17%</td>
</tr>
<tr>
<td>Lymphopenia*</td>
<td>51%</td>
<td>18%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>42%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36%</td>
<td>2%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>32%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>24%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26%</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21%</td>
<td>-</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>52%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13%</td>
<td>-</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>35%</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26%</td>
<td>1%</td>
</tr>
<tr>
<td>Edema</td>
<td>15%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Table 7: Adverse Reactions, cont’d

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADCETRIS + CHP Total N = 223 % of patients</th>
<th>CHOP Total N = 226 % of patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>26%</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>16%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>Cough</td>
<td>13%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>12%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>11%</td>
<td>-</td>
</tr>
</tbody>
</table>

*Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and of end of treatment. The table includes a combination of grouped and ungrouped terms. CHP – cyclophosphamide, doxorubicin, and prednisone; CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone. Events were graded using the NCI-CGTAE Version 4.03.

Additional Important Adverse Reactions

Infusion Reactions

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), infusion-related reactions were reported in 10 patients (4%) in the ADCETRIS + CHP-treated arm: 2 (1%) patients with events that were Grade 3 or higher events, and 8 (4%) patients with events that were less than Grade 3.

Pulmonary Toxicity

In a trial in patients with CHL that studied ADCETRIS with bortezomib as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (labetalol, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea, interstitial infiltration and/or inflammation were observed on radiographs and computed tomography imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bortezomib is contraindicated.

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADCETRIS + CHP arm; all events were pneumonitis.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure, Blood and lymphatic system disorders: febrile neutropenia. Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes). Hepatobiliary disorders: hepatotoxicity. Infections: PVF, serious infections and opportunistic infections. Metabolism and nutrition disorders: hyperbilirubinemia. Respiratory, thoracic and mediastinal disorders: non-infectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes). Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising 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 to ADCETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.
Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 158 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (92%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MVA2, which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Drug Risk Summary: ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations. See Data. The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a fetus.

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

Data

Animal Data

In an embryofetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1.3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 8 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (>99%), postimplantation loss (>99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and martinated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary: There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from ADCETRIS, including cytokines and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential

• ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action.

• Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

• Contraception

• Females: Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

• Males: ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

• Infertility

• Males: Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with CHOP for patients with previously untreated, CD30-expressing PTCL, 81% of ADCETRIS + CHOP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions (Grade 3 and 4) and 49% had serious adverse reactions. Among patients younger than age 65, 82% had adverse reactions (Grade 3 and 4) and 33% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CrCl <30 mL/min). No dosage adjustment is required for mild (CrCl 30–50 mL/min) or moderate (CrCl 15–30 mL/min) renal impairment.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy: Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness.

Fever/Neutropenia: Advise patients to contact their health care provider if a fever of 100.3°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

Infection Reactivation: Advise patients to contact their health care provider if they experience signs and symptoms of infection reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

Hepatotoxicity: Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Progressive Multifocal Leuкоencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:

• Changes in mood or unusual behavior
• Confusion, thinking problems, loss of memory
• Changes in vision, speech, or walking
• Decreased strength or weakness on one side of the body

Pulmonary Toxicity: Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

Acute Pancreatitis: Advise patients to contact their health care provider if they develop severe abdominal pain.

Gastrointestinal Complications: Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise patients to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcertris.com

Seattle Genetics

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TREMENDOUS PROGRESS HAS BEEN made to understand the strategies that can be used to overcome ESR1 mutations in estrogen receptor (ER)-positive breast cancer, and potent selective ER modulators (SERMs) may be the key to combat these mutations, according to Debu Tripathy, MD.

“The [degree] to which [SERMs] can reverse resistance probably depends on many aspects of the agent,” Tripathy said. “These need to be formally studied not just in the laboratory but [also] in clinical trials. We are starting to get some hints of that [work], but it’s just the beginning.”

ESR1 mutations generally arise following treatment with an aromatase inhibitor (AI), Tripathy explained, so acquiring genomic information after a patient progresses is critical to inform treatment selection.

The novel SERM lasofoxifene is being investigated in combination with the CDK4/6 inhibitor abemaciclib (Verzenio) in the phase 2 ELAINEII trial (NCT04432454) in patients with advanced or metastatic ER-positive, HER2-negative breast cancer whose tumors harbor an ESR1 mutation. In May 2019, the FDA granted fast track designation to lasofoxifene for the treatment of female patients with ER-positive, HER2-negative metastatic, ESR1-mutant breast cancer.1

In an interview with OncologyLive®, Tripathy, professor and chair of the Department of Breast Medical Oncology, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center in Houston, discussed the role of CDK4/6 inhibitors in ER-positive, HER2-negative breast cancer, the emergence of SERMs, and the growing understanding of ESR1 mutations in this space.

Resistance to frontline therapy with a CDK4/6 inhibitor plus endocrine therapy is an area of ongoing research. Is there reason to believe that patients could have nonoverlapping sensitivities to CDK4/6 inhibitors?

When patients progress on a CDK4/6 inhibitor, I will generally discontinue the use of CDK4/6 inhibitors. No clear data [show] that patients who become resistant [to a CDK4/6 inhibitor] may be sensitive to other [CDK4/6] inhibitors; however, some anecdotal data from individual hospital series suggest there could be some nonoverlapping sensitivity.

However, we have many other options, which is why I will generally move on to another form of therapy. We need to formally study the impact of one CDK4/6 inhibitor after progression on another because we may find that some of these agents perform better in that setting.

Do you order tumor profiling after each progression?

I tend to get genomics at the very beginning when patients [receive a new diagnosis], although I may not use that information in the first-line setting. However, it is good to have [the genomic information], especially for truncal mutations. [Truncal mutations, such as PIK3CA mutations,] tend to be prevalent in most of the cells. ESR1 mutations tend to be subclonal and may not be present [up front] but may arise later after the patient has been on an [AI].

If I haven’t [obtained genomic information] at the beginning, I will certainly get it at the time of progression on first-line therapy.

How do ESR1 mutations differ from other somatic mutations?

ESR1 mutations tend to arise in the presence of pretreatment, particularly with estrogen-deprivation therapy, which, pharmacologically, would be AIs. The Cancer Genome Atlas published [results stating] that ESR1 mutation rates were very low, perhaps 1% or so at diagnosis and based on the patient’s primary tumor. However, [ESR1 mutations arise] after exposure to AIs.

That makes sense because AIs work by depriving estrogen from the environment. To be activated, ERs need to bind to estrogen. So [AIs] select for any mutations that may

**FIGURE.** ELAINEII Trial Schema

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Pre- (with ovarian suppression) and postmenopausal women with MBC who progressed on either first- or second-line hormonal treatment with or without a CDK4/6 inhibitor including an AI or fulvestrant</td>
</tr>
<tr>
<td>– If possible, a biopsy of metastatic breast cancer tissue should be obtained to provide histological or cytological confirmation of ER+/HER2- disease</td>
</tr>
<tr>
<td>– Lesions measurable by RECIST 1.1 or nonmeasurable lesions</td>
</tr>
<tr>
<td>– ESR1 point mutations as assessed in cell-free ctDNA</td>
</tr>
<tr>
<td>– ECOG performance status 0 or 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-mg oral lasofoxifene once daily plus 150-mg oral abemaciclib twice daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Secondary</td>
</tr>
<tr>
<td>PFS</td>
</tr>
<tr>
<td>CBR</td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>DOR</td>
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<tr>
<td>Time to response</td>
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</tbody>
</table>

AI, aromatase inhibitor; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; DOR, duration of response; MBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival.
occur where a mutation [is present] in the ER that allows it to be activated without the presence of estrogen; that is what most activating ESR1 mutations do. Specifically, upon exposure to AIs is when we start to see these mutations arise.

**At the virtual 2020 American Association for Cancer Research Annual Meeting, investigators from The University of Chicago presented a poster on in vivo data looking at lasofoxifene alone and in combination with palbociclib [Ibrance] versus fulvestrant. What did we learn from these data and how could they potentially translate to the clinic?**

 Those data are compelling. They show that we can get growth inhibition in ESR1 mutations and that it can be potentially aided with CDK4/6 inhibitors. I have seen examples of this and other data that show [tumor growth] can be reversed in cell-line models.

 What we see in those cell-line models—even in animal models, which are more accurate but may not be the whole story—may not turn out to be the case in the tumor microenvironment and all of the other factors involved. Therefore, although this is very supportive and raises enthusiasm for getting these types of drugs into clinical trials, we need to wait to see what happens when patients are taking these drugs.

**ELAINE set the stage for ELAINEII (FIGURE 2), evaluating lasofoxifene plus abemaciclib. What is the anticipated impact of the ELAINEII trial?**

 The ELAINE trial compared fulvestrant with lasofoxifene in patients with ESR1 mutations. It’s a direct test of the hypothesis that [lasofoxifene] may be more favorable than [fulvestrant], which we now consider a reasonable drug to use when we see ESR1 mutations or in the second line in general.

 ELAINEII is designed to...combine [lasofoxifene] with a CDK4/6 inhibitor. It will allow patients who have [had] prior [treatment with] CDK4/6 inhibitors [to enroll]. There is some anecdotal evidence that responses have been seen with abemaciclib after progression on other CDK4/6 inhibitors.

 The approval of abemaciclib was based on a trial results that showed responses in refractory hormone receptor-positive disease as a single agent, but those patients had not been previously exposed to CDK4/6 inhibitors. We believe that the combination of these 2 different strategies could bring about more responses and longer time to progression.

**The PARSIFAL trial (NCT02491983) did not look at lasofoxifene, but rather an AI plus palbociclib versus fulvestrant. How could those findings potentially affect the landscape?**

 One of the issues [in this treatment landscape] is pairing CDK4/6 inhibitors with different endocrine therapies; we haven’t formally compared [those regimens]. We do know from the FALCON trial [data (NCT01602380)] that when using endocrine therapies alone fulvestrant is slightly better than AI therapy, particularly in patients who haven’t been treated before or have nonvirocebral disease. Then the MONALEESA-3 study [NCT02422615] took advantage of the FALCON findings and compared treatment with fulvestrant alone versus fulvestrant plus ribociclib [Kisqali], regardless of first- or second-line therapy. That study showed a significant improvement in outcomes with a hazard ratio of around 0.5, which has been seen before.

 The PARSIFAL trial, on the other hand, was a direct comparison [of an AI or fulvestrant] with palbociclib. The trial did not show a difference in progression-free survival. We are left without knowing what population fulvestrant might be best for, but [we have the knowledge that] fulvestrant is certainly a reasonable option in the first- or second-line setting. We have fewer data regarding what to do in the second line for patients who received fulvestrant up front, but [data from] the PARSIFAL and MONALEESA-3 studies showed that [ribociclib and palbociclib] are both reasonable agents to use and could be building blocks for [combinations] with other targeted agents.

**How do you anticipate genomic classification will continue to affect the research landscape?**

 The [further] subclassification of breast cancer is very important in general. In breast cancer, not all patients with luminal A or luminal B [disease] are the same. There may be certain aspects about the different pathways involved in growth and other cellular functions, such as invasion and apoptosis, that may vary depending on different gene profiling. Gene profiling is basically a way...
to categorize cancers, but if we can categorize them in functionally relevant ways, then we are really making advances.

This takes studying large numbers of patients, ideally in the context of a clinical trial where they are being treated similarly or we are comparing 1 treatment with another. Then we can dissect the different molecular profiles that may predict a benefit. More importantly, we can use that information about the molecular profiles to identify mechanisms of resistance that could inform newer strategies.

**What other ongoing research is needed in the ESR1-mutant breast cancer space?**

Not all mutations are the same. There may be certain ESR1 mutations that are generated in certain situations and under certain treatments that we need to understand better. What is really fascinating is trying to understand the functional consequences of ESR1 mutations, not only in terms of proliferation, but in terms of many other phenotypes that we are interested in targeting, such as metabolic activity, DNA repair, or other hallmarks of cancer. [Knowing] whether it is invasion, the ability to resist apoptosis, or immunogenicity is critical. Studies in the basic aspects of what ERS1 mutations do [are important]. [Also, evaluation of] the nitty gritty molecular structure and how the ER interacts with coactivators, corepressors, and other aspects of the transcriptional machinery that make the ER work [is needed] to understand what ESR1 does.

Of course, we are aware of many other mutational isoforms, such as RAS mutations and growth factor mutations, such as exon 20. We need to understand the inner workings of what these mutations cause. When you think about it, cancer is selection of the fittest. Cancer cells have a higher mutational rate. Many of the mutations that arise out of accident lead to cell death. However, it is those that lead to cell advantage that perpetuate. By understanding the most common driver mutations that arise over time, we can start to develop therapies against each one…. There will always be rare mutations that are going to be more difficult to understand and target.

**REFERENCES**


2. Damodaran S, Plourde PV, Tripathy D, Jenkins S, Portman D. An open-label, multicenter study evaluating the safety of lasofoxifene in combination with abemaciclib for the treatment of pre- and postmenopausal women with locally advanced or metastatic ER+/HER2- breast cancer and ESR1 mutation. Poster presented at: 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Poster OT-09-01

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Coleman Looks Forward to a Big Year for New Cervical Cancer Therapies

by DENISE MYSHKO

FIVE NEW THERAPIES FOR the treatment of patients with cervical cancer are in late-stage development that could potentially change clinical practice and set the stage for 2021 to be a banner year for FDA approvals for this malignancy, according to Robert L. Coleman, MD.

“This is going to be really exciting,” said Coleman, noting that there have been only 2 new drug approvals for cervical cancer in recent years: bevacizumab (Avastin) plus chemotherapy in 2014 and pembrolizumab (Keytruda) for PD-L1 positive disease in 2018.1,2

Coleman, a 2020 Giants of Cancer Care® award winner in the gynecologic malignancies category, identified the following therapies as among the most promising in the cervical cancer pipeline: lifileucel; balstilimab as a single agent and in combination with zalifrelimab; tisotumab vedotin; cemiplimab-rwlc (Libtayo); and pembrolizumab (Keytruda) in combination with chemotherapy (TABLE).

In an interview with OncologyLive®, Coleman discussed key data for these therapies and touched on emerging developments concerning new therapies in ovarian and endometrial cancers. Coleman, a longtime clinical investigator and leader of the Gynecologic Oncology Group Foundation, became chief scientific officer of The US Oncology Network in March 2020.

LATE-STAGE CERVICAL CANCER CANDIDATES

Lifileucel, formerly known as LN-145, uses autologous tumor-infiltrating lymphocytes (TILs) harvested from tumor fragments to create a patient-specific immunotherapy. In November 2020, Iovance Biotherapeutics, Inc, which is developing the adoptive cell transfer therapy, said the last patient has been dosed in the pivotal cohort of the phase 2 C-145-04 trial (NCT03108495) in patients with recurrent, metastatic, or persistent cervical cancer. The company is discussing assays to define TILs with the FDA and plans to submit a biologics license application (BLA) to the agency this year.3

In early findings from the pivotal trial, lifileucel demonstrated a 44% objective response rate (ORR) among 27 patients, including 3 complete responses (11%) and 9 partial responses (33.3%), for an 85% disease control rate, according to data presented at the 2019 American Society of Clinical Oncology Annual Meeting.4 TIL persistence was observed at 6 months in the peripheral blood mononuclear cells of 20 participants available for analysis, suggesting that memory T cells in the TIL therapy can be long lived, investigators said in a poster presented at the European Society for Medical Oncology Virtual Congress 2020 (ESMO 2020).5

Another treatment moving forward in the regulatory process is balstilimab, an anti-PD-1 monoclonal antibody. In September 2020, Agenus Inc, the drug’s developer, started a rolling BLA with the FDA for use of balstilimab in recurrent or metastatic cervical cancer based on findings from a single-arm phase 2 trial (NCT03104699).6 The study enrolled patients with squamous cell, adenosquamous, or adenocarcinoma of the cervix who had relapsed or progressed on or after platinum-based treatment. Balstilimab monotherapy resulted in a 14% ORR among 160 patients in the intention-to-treat population, with a median duration of response (DOR) of 15.4 months (range, 1.1+ to 15.4), according to findings presented at ESMO 2020. The ORR was 19% among participants with PD-L1-positive tumors (19 of 99 patients).7

In a separate phase 2 trial (NCT03495882), balstilimab administered in combination with zalifrelimab, a CTLA-4 inhibitor, resulted in an ORR of 22% among 143 patients, with the median DOR not reached (range, 1.3+ to 16.6+ months). The ORR was 27% among those with PD-L1-positive disease (21 of 79 patients).8 The combination is being developed under an FDA fast track designation.9

Tisotumab vedotin, another therapy on the horizon, is an antibody-drug conjugate that targets tissue factor, part of the coagulation network, which is highly prevalent in cervical cancer and other solid tumors. Coleman and colleagues presented data at ESMO 2020 from the phase 2 innovaTV 204 trial (NCT03438396) evaluating tisotumab vedotin as monotherapy, if appropriate, in patients with recurrent or extrapelvic metastatic cervical cancer that progressed during or after doublet chemotherapy with bevacizumab.9

<table>
<thead>
<tr>
<th>TABLE. Emerging Therapies for Cervical Cancer</th>
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<tbody>
<tr>
<td>Agent</td>
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<tr>
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</tr>
<tr>
<td>Lifileucel</td>
</tr>
<tr>
<td>Balstilimab</td>
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<tr>
<td>Tisotumab vedotin</td>
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<tr>
<td>Cemiplimab-rwlc (Libtayo)</td>
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<tr>
<td>Pembrolizumab (Keytruda)</td>
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ADC, antibody-drug conjugate; BLA, biologics license application; TIL, tumor-infiltrating lymphocyte.
The ORR was 24% (95% CI, 15.9-33.3) among 101 patients who received tisotumab vedotin, including 7 patients (7%) with a complete response and 17 patients (17%) with a partial response. After a median follow-up of 10 months, the median DOR was 8.3 months (95% CI, 4.3-not reached). The median time to response was 1.4 months (range, 1.1-5.1), with activity generally observed within the first 2 treatment cycles.2

Plans call for the phase 3 innovaTV 301 trial (NCT04697628) to start enrolling patients in January 2021. The study will evaluate tisotumab vedotin monotherapy versus physician’s choice of 1 chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) as second- or third-line treatment for patients with recurrent or metastatic cervical cancer. The trial aims to enroll 482 participants.

Several immune checkpoint inhibitors approved in other indications also are being investigated for cervical cancer. Cemiplimab, a PD-1 inhibitor approved for patients with metastatic or locally advanced cutaneous squamous cell carcinoma, is being evaluated in a phase 3 trial (NCT03257267) as monotherapy versus physician’s choice of chemotherapies in patients with recurrent or metastatic platinum-refractory cervical cancer with squamous cell histology.

In November 2020, investigators reported data from expansion cohorts from a phase 1 trial (NCT02383212) that evaluated cemiplimab as a monotherapy or in combination with hypofractionated radiation therapy in patients with recurrent or metastatic cervical cancer. One of the 10 patients in each cohort achieved a partial response for an ORR of 10% (95% CI, 0.3%-44.5%); both responders had squamous histology. The DOR was 11.2 months and 6.4 months in the monotherapy and combination cohort, respectively.10

“In cervix cancer recurrence, if the cemiplimab trial is positive, that would replace chemotherapy with an immune checkpoint inhibitor. We’re monitoring these phase 3 studies that could be reporting in 2021,” Coleman said.

These studies include the phase 3 KEYNOTE-826 trial (NCT03635567), which is testing the PD-1 inhibitor pembrolizumab in combination with investigator’s choice of chemotherapy (paclitaxel plus either cisplatin or carboplatin) with bevacizumab, if appropriate, versus chemotherapy with bevacizumab alone as first-line treatment for patients with persistent, recurrent, or metastatic cervical cancer. Pembrolizumab currently is approved for PD-L1-positive recurrent or metastatic cervical cancer that has progressed on or after chemotherapy.2

**OTHER MALIGNANCIES**

In the ovarian cancer space, Coleman said, the results of the TRUST trial (NCT02828618) could be practice changing. The trial is comparing primary debulking surgery followed by 6 cycles of standard chemotherapy versus 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery in patients with newly diagnosed invasive stage IIIB to IVC epithelial ovarian cancer. The study, which is designed for an enrollment of nearly 800 patients, is taking place at 20 centers with a high level of surgical expertise in ovarian cancer.

“This trial is going to be really important from a practice-changing standpoint because if it validates that there is no difference between those 2 modalities, then neoadjuvant chemotherapy will become an even bigger standard. If it refutes it, then it is going to change the way people look at surgical candidacy in ovarian cancer, and that will be practice changing,” Coleman said.

Coleman also is anticipating the results of the phase 3 ATHENA trial (NCT03522246), which is testing the combination of the PD-1 inhibitor nivolumab (Opdivo) plus the PARP inhibitor rucaparib (Rubraca) as maintenance therapy for patients who have responded to frontline platinum-based chemotherapy and have completed cytoreductive surgery. The study, which aims to enroll 1000 patients, has 4 arms: intravenous (IV) nivolumab plus oral rucaparib or placebo, rucaparib plus IV placebo, and an oral placebo plus an IV placebo. The primary end point is progression-free survival, and secondary end points include overall survival, ORR, and DOR.

“There are a lot of drug combinations that are working their way through [the pipeline], as well as novel treatments, including tumor treatment fields to novel biologics to gene therapy. PARP inhibitors will continue to roll out. We’ll have OS data starting to emerge on some of the mature trials. The exciting story for PARP inhibitors in 2021 is combinations,” Coleman said.

In endometrial cancer, Coleman hopes to see data this year from the phase 3 LEAP-001 trial (NCT03884101), which is studying the combination of pembrolizumab plus lenvatinib (Lenvima) versus the chemotherapy regimen of paclitaxel plus carboplatin.

“This will be important to see if we can replace chemotherapy in the metastatic, recurrent space,” he said. ■

**REFERENCES**


Vemurafenib Triplet Improves PFS in BRAF-Mutant Metastatic CRC

**by HAYLEY VIRGIL**

**THE ADDITION OF VEMURAFENIB**
(Zelboraf) to irinotecan (Onivyde) and cetuximab (Erbitux) led to a significant improvement in progression-free survival (PFS) versus irinotecan and cetuximab alone in patients with BRAF V600E-mutated metastatic colorectal cancer (CRC) whose tumors did not harbor NRAS or KRAS mutations, according to results of the SWOG S1406 study published in the *Journal of Clinical Oncology.*

The 3-drug combination reduced the risk of disease progression or death by 50% in this patient population (HR, 0.50; 95% CI, 0.32-0.76; *P* = .001). The median PFS was 4.2 months with the triplet versus 2.0 months with the doublet. Moreover, 80% of patients in the experimental arm had not progressed at week 9 compared with 39% of those in the control arm.

The triplet regimen also elicited a higher overall response rate (ORR) compared with the doublet regimen, at 17% and 4%, respectively (*P* = .05). The disease control rates in the experimental and control arms were 65% and 21%, respectively.

Forty-two percent of the patients on the control arm (n = 21) crossed over to receive the vemurafenib-containing regimen following disease progression. No significant difference in overall survival (OS) benefit was observed between the 2 treatment arms (HR, 0.77; 95% CI, 0.50-1.18; *P* = .23). Following crossover, the median PFS was 5.4 months in the cohort, with a response rate of 19% and a disease control rate of 76%.

The triplet regimen combines inhibition of BRAF and EGFR signaling with vemurafenib and cetuximab, respectively, with the chemotherapeutic irinotecan. The strategy is similar to the approach used in the phase 3 BEACON CRC trial (NCT02928224), which combined cetuximab with encorafenib (Braftovi), a BRAF inhibitor; and binimetinib (Mektovi), a MEK inhibitor.

“1-2-3 action, that triple threat, shuts off a powerful growth pathway in these cancers,” Scott Kopetz, MD, PhD, lead author of the study and a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, stated in a press release. “In this trial, unlike in BEACON, we added chemotherapy and found that it makes for a more effective way to treat this aggressive form of CRC.”

For SWOG S1406 (NCT02164916), patients were required to have histologically or cytologically confirmed metastatic or locally advanced or unresectable, BRAF V600E–mutant adenocarcinoma of the colon or rectum.

Patients with brain metastases were permitted for inclusion if they had received acceptable treatment with radiotherapy or surgery and achieved stability at least 90 days prior to initial registration. Participants were allowed to undergo 1 to 2 prior lines of therapy with chemotherapy for metastatic disease, but previous treatment with EGFR, BRAF, or MEK inhibitors was not permitted.

In the open-label phase 2 study, patients were randomized 1:1 to receive either the triplet or doublet regimen. Patients were stratified based on whether they had previously undergone treatment with irinotecan. Both cohorts were administered 180 mg/m² of irinotecan and 500 mg/m² of cetuximab intravenously every 2 weeks. Patients who received the triplet regimen also received a 960-mg dose of oral vemurafenib.

The primary end point of the study was PFS per local evaluation by the investigator. Key secondary outcomes included toxicity, OS, ORR, and PFS in patients who crossed over from the doublet arm to the triplet arm after experiencing disease progression.

Seventeen percent of patients (11 of 66), harbored *PIK3CA* mutations, which were found to be associated with a numeric improvement in PFS (HR, 0.3) versus the PFS benefit in those with wild-type disease (HR, 0.6); however, investigators noted that the study’s sample size precludes definitive conclusions. Additionally, patients were able to achieve clinical benefit regardless of microsatellite instability-high status, which 18% of patients (13 of 72) had.

Circulating tumor DNA (ctDNA) was evaluable in 69 patients, with 61 samples testing positive for *BRAF* V600E mutations at a median variant allele fraction (VAF) of 5.0% (range, 0.06%-49.6%) and a sensitivity of 88% (95% CI, 78%-95%). “Serial ctDNA testing of *BRAF* V600E has been previously validated as a sensitive marker of treatment response,” Kopetz and colleagues wrote. “In patients with at least 2 ctDNA time points, 87% demonstrated a reduction in VAF of *BRAF* V600E in the experimental arm, whereas no patients in the control arm demonstrated reduction in ctDNA levels.”

Regarding safety, grade 3 and 4 adverse effects (AEs) were more frequently reported in the triplet arm compared with the doublet arm; these toxicities included neutropenia (30% vs 7%, respectively), anemia (13% vs 0%), and nausea (19% vs 2%).

“The addition of vemurafenib to cetuximab and irinotecan represents an active combination that improves PFS,” the authors concluded. “This represents a rationally designed study building on a foundation of understanding of the mechanisms of adaptive resistance in CRC and provides insights for further combination studies in the CRC field in the future.”

**REFERENCES**

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

Patients may qualify to participate in the study if they:

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

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

Visit www.elainestudy.com to Learn More

*Als include Arimidex (anastrozole), Femara (letrozole), or Aromasin (exemestane). CDK 4/6 inhibitors include Kisqali (ribociclib), Ibrance (palbociclib), and Verzenio (abemaciclib).
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ER, estrogen receptor; HER, human epidermal receptor.
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EXCITEMENT TOOK WING IN the scientific community in the early 1990s, when the first gene therapy trial showed significant success, only to crash at the end of the decade with a patient’s tragic death.

Twenty years later, the excitement is back and greater than before. Although safety remains a concern, investigators are breaking ground in cell and gene therapy, and many believe that ultimately, a string of cured cancers will follow.

In 2017, the excitement over these therapies returned in spades when the FDA signed off on a cell-therapy drug for the first time, approving the chimeric antigen receptor (CAR) T-cell treatment tisagenlecleucel (Kymriah; Novartis) for patients with B-cell precursor acute lymphoblastic leukemia. At last, scientists had devised a way to reprogram a person’s own T cells to attack tumor cells.

“We’re entering a new frontier,” said Scott Gottlieb, MD, then-FDA commissioner, in announcing the groundbreaking approval.

Gottlieb was not exaggerating. The growth in CAR T-cell research is exploding. Although only a handful of cell and gene therapies are on the market, the FDA predicted in 2019 that it will receive more than 200 investigational new drug applications per year for cell and gene therapies, and that by 2025, it expects to have accelerated to 10 to 20 cell and gene therapy approvals per year.

“We can absolutely cut the number of cancer deaths down so that one day in our lifetimes it can be a rare thing for people to die of cancer,” said Patrick Hwu, MD, president and CEO of Moffitt Cancer Center in Florida and among gene therapy’s pioneers. “It still may happen here and there, but it’ll be kind of like people dying of pneumonia. It’s like, ‘He died of pneumonia? That’s kind of weird.’ I think cancer can be the same way.”

“Essentially, you can kill any cancer cell that has an antigen that is recognized by the immune cell,” Hwu said. “The key to curing every single cancer, which is our goal, is to have receptors that can recognize the tumor but don’t recognize the normal cells.”

IMPlications FOR THE COMMUNITY ONCOLOGIST
Community oncologists will need to be increasingly familiar about the various products, including their immediate and longer-term risks, Bo Wang, MD, and Deepu Madduri, MD, recently wrote in OncologyLive®.1 “It is key to understand the optimal time for referring these patients to an academic institution, as well as how to manage the requisite post CAR T-cell therapy in the community setting.” Madduri is an assistant professor of medicine, hematology and medical oncology, as well as associate director of cellular therapy service, and director of clinical operations with the Center of Excellence for Multiple Myeloma at The Tisch Cancer Institute and the Icahn School of Medicine at Mount Sinai in New York, New York. Wang is a third-year clinical fellow in hematology/oncology at Mount Sinai.

Early referral to academic centers and hospitals equipped to deliver therapies is crucial for patients eligible for therapy. However, as advances continue in the field, community practices may be called upon to administer therapies in their clinic.

The Community Oncology Alliance (COA) envisions a broader role for the settings in which CAR T-cell therapies can be administered. When the Centers for Medicare & Medicaid Services (CMS) was considering coverage for CAR T-cell therapies in 2019, COA officials argued against limiting approvals to hospitals.

“It is important to understand that there are state-of-the-art community oncology practices that have significant experience and capabilities in administering highly complex treatments,” COA officials wrote in a letter to CMS. “For example, stem cell transplants, which are similar in complexity to CAR T therapy, are performed successfully in the community oncology practice setting.”2

Broader use of gene therapies depends on several factors, including navigating the logistics of gene therapies, addressing the high costs, and managing toxicities.3
Autologous CAR T-cell therapies involve a manufacturing process that requires coordination between the treating facility and the processing facility. Following leukapheresis, patients may require maintenance therapy to control disease progression during the manufacturing time, which can take 3 to 5 weeks. In terms of cost, gene and cell therapies can cost from $375,000 to $475,000 per dose and they may face coverage restrictions from payers. Approvals could take weeks to obtain.3,4

Because of cytokine release syndrome and neurotoxicities associated with CAR T-cell therapy, the FDA mandates risk evaluation and mitigation strategy training for centers.

Further, providers may find that real-world experiences with gene therapies are different from those seen in the clinical trial setting, according to Ankit J. Kansagra, MD.

In a presentation at the 2020 American Society of Clinical Oncology Virtual Education Program, Kansagra, an assistant professor of medicine and Eugene P. Frenkel, MD, Scholar in Clinical Medicine at Harold C. Simmons Comprehensive Cancer Center in Dallas, Texas, said that in practice patients may be older and have more aggressive disease, with double- and triple-hit lymphomas.4

Specifically, Kansagra noted that medications such as steroids and/or tocilizumab (Actemra) to prevent or treat cytokine release syndrome or other toxicities were more frequently used in the real-world setting than what had been seen in clinical trials.

As it stands now, only a fraction of eligible patients are receiving CAR T-cell therapies, Kansagra said. Potentially, 9750 patients a year may be eligible for CAR T-cell therapies in approved and upcoming hematologic indications. From 2016 to 2019, a total of 2058 patients received CAR T-cell infusion.4

Next steps for transplanting these novel therapies to clinical practice will require changes in key areas, Kansagra said, such as supply chain management, patient support, and financial systems (FIGURE).4

Meanwhile, multiple myeloma experts advise providers to be ready for change. “As commercially available myeloma CAR T-cell therapies are approved, it will be even more important for community oncologists to better understand these therapies so they can offer them to their patients,” Wang and Madduri wrote.1

### ENGINEERING CHANGE

Cell therapy involves cultivating or modifying immune cells outside the body before injecting them into the patient. Cells may be autologous (self-provided) or allogeneic (donor-provided); they include hematopoietic stem cells and adult and embryonic stem cells. Gene therapy modifies or manipulates cell expression. There is considerable overlap between the 2 disciplines.

Juliette Hordeaux, PhD, senior director of translational research for the University of Pennsylvania’s gene therapy program, is cautious about the FDA’s predictions, saying she’d be “thrilled” with 5 cell and/or gene therapy approvals annually.

“For monogenic diseases, there are only a certain number of mutations, and then we’ll plateau until we reach a stage where we can go after more common diseases,” Hordeaux said.

“Safety has been the main brake around aden-associated virus vector [AAV] gene therapy,” added Hordeaux, whose hospital’s program has the institutional memory of both Jesse Gelsinger’s tragic death during a 1999 gene therapy trial as well as breakthroughs by 2015 Giants of Cancer Care.6

The number of clinical trials evaluating CAR T-cell therapies has risen sharply since 2015, when investigators counted a total of 78 studies registered on the ClinicalTrials.gov website. In June 2020, the site listed 671 trials, including 357 registered in China, 256 in the United States, and 58 in other countries.6 Natural killer (NK) cells are the research focus of Dean A. Lee, MD, PhD, a physician in the Division of Hematology and Oncology at Nationwide Children’s Hospital in Columbus, Ohio. He developed a method for consistent, robust expansion of highly active clinical-grade NK cells that enables repeated delivery of large cell doses for improved efficacy. This finding led to several first-in-human clinical trials evaluating adoptive immunotherapy with expanded NK cells under an FDA investigational new drug application. Lee is developing both genetic and

### FIGURE. Next Steps for Effective Delivery of Gene and Cell Therapies

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<thead>
<tr>
<th>SUPPLY CHAIN MANAGEMENT</th>
</tr>
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<tbody>
<tr>
<td>Commercial scalability</td>
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<td>Academic manufacturing</td>
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<tr>
<th>PATIENT SUPPORT</th>
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<td>Wait during cell processing</td>
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<tr>
<td>Transportation challenges and care delivery availability</td>
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<th>THERAPY DELIVERY ECONOMICS</th>
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<tr>
<td>Reimbursement</td>
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<td>Payment structure</td>
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**SUPPLY CHAIN MANAGEMENT**

- Commercial scalability
- Academic manufacturing

**PATIENT SUPPORT**

- Access to gene therapies
- Wait during cell processing
- Transportation challenges and care delivery availability

**THERAPY DELIVERY ECONOMICS**

- Reimbursement
- Payment structure

**ENGINNERING CHANGE**

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nongenetic methods to improve tumor targeting and tissue homing of NK cells. His efforts are geared toward pediatric sarcomas.

“The biggest emphasis over the past 20 to 25 years has been cell therapy for cancer, talking about trying to transfer a specific part of the immune system for cells,” said Lee, who is also director of the Cellular Therapy and Cancer Immunology Program at Nationwide Children’s Hospital, at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital, and at the Richard J. Solove Research Institute.

COVID-19 AND OTHER DISEASES

However, Lee said, NKs have wider potential. “This is kind of a natural swing back. Now that we know we can grow them, we can reengineer them against infectious disease targets and use them in that [space],” he said.

Lee is part of a coronavirus disease 2019 (COVID-19) clinical trial, partnering with Kiadis, for off-the-shelf K-NK cells using Kiadis’ proprietary platforms. Such treatment would be a postexposure preemptive therapy for treating COVID-19. Lee said the pivot toward treating COVID-19 with cell therapy was because “some of the very early reports on immune responses to coronavirus, both original [SARS-CoV-2] and the new [mutation], seem to implicate that those who did poorly [overall] had poorly functioning NK cells.”

The revolutionary gene editing tool CRISPR is making its initial impact in clinical trials outside the cancer area. Its developers, Jennifer Doudna, PhD, and Emmanuelle Charpentier, PhD, won the Nobel Prize in Chemistry 2020.

For patients with sickle cell disease (SCD), CRISPR was used to reengineer bone marrow cells to produce fetal hemoglobin, with the hope that the protein would turn deformed red blood cells into healthy ones. National Public Radio (NPR) did a story on one patient who, so far, thanks to CRISPR, has been liberated from the attacks of SCD that typically have sent her to the hospital, as well from the need for blood transfusions.

“It’s a miracle, you know?” the patient, Victoria Gray of Forest, Mississippi, told NPR.

She was among 10 patients with SCD or transfusion-dependent beta-thalassemia treated with promising results, as reported by the New England Journal of Medicine.

Stephen Gottschalk, MD, chair of the department of bone marrow transplantation and cellular therapy at St Jude Children’s Research Hospital, said, “There’s a lot of activity to really explore these therapies with diseases that are much more common than cancer.”

Animal models use T cells to reverse cardiac fibrosis, for instance, Gottschalk said. Using T cells to reverse pathologies associated with senescence, such as conditions associated with inflammatory clots, are also being studied.

“CAR T, I think, will become part of the standard of care,” Gottschalk said. “The question is how to best get that accomplished. To address the tribulations of some autologous products, a lot of groups are working with off-the-shelf products to get around some of the manufacturing bottlenecks. I believe those issues will be solved in the long run.”

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

Biden Issues Health Care Executive Orders

by KEITH A. REYNOLDS

THE NEWLY MINTED FEDERAL administration wasted no time in enacting its health care agenda, as President Joseph R. Biden signed a flood of executive orders during his first 48 hours in office. While many seek to roll back actions taken by his predecessor, the nation’s coronavirus disease 2019 (COVID-19) response seems to be a top priority as well. Here’s a look at some of Biden’s early actions:

► Improving and expanding access to COVID-19 care and treatments—This order directs officials to support studies and trials for new COVID-19 interventions, create recommendations for expanding health care facility capacity, and improve access to quality and affordable treatments.

► Data-driven response to COVID-19—The heads of all executive departments and agencies are ordered to help in the gathering and dissemination of all COVID-19 data in order to assist in the response to the pandemic and in enhancing the data collection and collaboration capabilities in these kinds of public health threats. This order also seeks to improve public health data collection and analytics going forward.

► Shoring up the public health supply chain—Biden invokes the Defense Production Act to inventory all COVID-19 response supplies, take steps to address pricing of pandemic response supplies, shore up the pandemic supply chain, and facilitate Indigenous peoples’ access to the strategic national stockpile.

► Protecting worker health and safety—Using the Occupational Safety and Health Act, the secretary of labor will issue revised guidance to employers in the next 2 weeks on workplace safety during the COVID-19 coronavirus pandemic.

These are just a sample of the actions taken. A fuller view of the new administration’s executive orders can be found in a fact sheet released by the White House.

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Monoclonal Antibodies Prove to Be Novel Therapeutics for Myeloma

by FRITS VAN RHEE, MD, PhD

MULTIPLE MYELOMA (MM) IS generally considered an incurable malignancy, although a proportion of patients may achieve long-term disease-free survival with a comprehensive and aggressive treatment approach.¹ The therapeutic armamentarium has rapidly expanded in recent years because of the approval of novel drugs such as carfilzomib (Kyprolis), ixazomib (Ninlaro), pomalidomide, daratumumab (Darzalex), and selinexor (Xpovio). Others, such as melflufen, likely will come to market in the near future. These drugs have especially improved the treatment options for relapsed disease, with some agents now also being used as frontline therapy. As a result, outcomes for patients with newly diagnosed and relapsed disease continue to improve with prolongation of median survival to greater than 7 years from diagnosis.

Immunotherapy holds great promise for the treatment of MM following the trends seen with developments in the lymphoma field. The addition of the anti-CD20 monoclonal antibody rituximab (Rituxan) to cyclophosphamide, doxorubicin hydrochloride (Adriamycin), vincristine sulfate (Oncovin), and prednisone has greatly improved the prognosis of lymphoma. Additionally, the antibody-drug conjugate (ADC) brentuximab vedotin (Adcetris) has had a similar impact on Hodgkin lymphoma. Innovative immunotherapeutics also are finding their way into the MM field and are set to have a transformative effect on the prognosis of both patients with transplant-eligible and ineligible MM with the possibility of the elusive goal of cure within the reach of many more patients in the not-too-distant future.

Immunotherapy for MM comprises exciting new agents, such as chimeric antigen receptor (CAR) T cells, “naked” antibodies, bispecific antibodies, ADCs, vaccines and new immunomodulatory agents such as the cereblon E3 ligase modulators (CELMoDs). Herein, the focus will be on the development of monoclonal antibody therapeutics.

NEWLY DIAGNOSED MM

The anti-CD38 monoclonal antibody daratumumab is approved as frontline therapy for patients with MM who are eligible based on data from the phase 3 Cassiopeia trial (NCT02541383). Investigators evaluated daratumumab (D) in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) versus VTd alone. Patients treated with D-VTd (n = 543) achieved a more frequent stringently defined complete remission compared with those treated with VTd (n = 542) at rates of 39% versus 26%, respectively. Patients also had higher rates of minimal residual disease negativity (64% vs 44%, respectively).²

In the GRIFFIN study (NCT02874742), investigators evaluated daratumumab with the lenalidomide, bortezomib, dexamethasone backbone (RVd) as induction and consolidation therapy in patients who were candidates for high-dose therapy with melphalan followed by stem cell transplantation. Overall, patients treated with D-RVd achieved a more frequently stringent complete response compared with those receiving standard RVd (62.6% vs 45.4%, respectively). Patients with standard cytogenetic risk (n = 79) were the principal beneficiaries of therapy with daratumumab (stringent complete response, 49.4%; OR, 2.03; 95% CI, 1.05-3.85).³

Data from the ongoing phase 3 PERSEUS registration study (NCT03710603) will determine whether subcutaneous formulation of daratumumab and hyaluronidase human-fij (Darzalex Faspro) in combination with RVd improves progression-free survival (PFS) in patients with transplant-eligible newly diagnosed MM. It seems likely that the quadruplet regimens of D-RVd and D-VTd will become the new standards of care as upfront therapy in MM. Daratumumab is approved for nontransplant-eligible disease in combination with lenalidomide and dexamethasone; bortezomib, melphalan, and prednisone; as well in the relapse setting in combination with bortezomib, lenalidomide, or pomalidomide.⁴⁻⁸

RELAPSED/REFRACTORY MM

A second anti-CD38 monoclonal antibody, isatuximab-irfc (Sarclisa), which has a somewhat different mechanism of action and recognizes a different epitope, was approved in 2020 for patients with relapsed/refractory MM based on data from the ICARIA-MM study (NCT02990338). Patients treated with isatuximab, pomalidomide, and dexamethasone had superior PFS compared with those who received pomalidomide and dexamethasone (11.5 vs 6.5 months, respectively).⁹

Elotuzumab (Empliciti) is a monoclonal antibody recognizing the cell surface glycoprotein SLAMF7 or CS1 that was approved for relapsed/refractory MM in combination with lenalidomide and dexamethasone.¹⁰ Data from the randomized phase 3 ELOQUENT-3 study (NCT02654132) showed that elotuzumab performed particularly well in combination with pomalidomide and dexamethasone (EPd). Patients in the EPd arm (n = 60) had significantly
higher overall response rates (53% vs 26%) and prolonged PFS (10.3 vs 4.7 months) compared with those who received Pd alone (n = 57).11

MOVING THE NEEDLE IN MM
A common theme of this class of antibodies is that these agents are generally well tolerated with manageable toxicities, are easily combined with existing agents, and can be given to elderly patients. It is also important to note that monoclonal antibodies such as daratumumab are used as an adjunct to melphalan-based stem cell transplantation in newly diagnosed patients. Future studies are needed to clarify whether these novel combinations can safely permit delayed transplantation or even avoid transplantation altogether.

A large number of bispecific antibodies are in clinical development for relapsed/refractory MM.12 Bispecific T-cell engagers (BiTEs) have dual antigen specificity. BiTEs bind to and activate T cells via the CD3/TCR receptor complex and link activated immune T effectors to MM cells by binding to a MM-associated tumor antigen. In comparison with CAR T cells, bispecific antibodies have advantages such as off-the-shelf use (which eliminates the need for a cellular manufacturing), immediate availability of the drug, and lack of need for lymphotoxic chemotherapy.

A disadvantage of bispecific antibodies is that they are ill-suit ed for heavily treated patients since their activity is critically dependent on the fitness of the patient’s immune cells. In addition, the short half-life requires continuous infusion and has been an issue in some studies. As with CAR T cells, bispecific antibodies can have significant adverse effects, including cytokine release syndrome and neurotoxicity. Most bispecific antibodies are directed at B-cell maturation antigen (BCMA); however, other targets are under investigation, including CD56, CD38, Fc receptor-like protein 5 (FCRL5), and G-protein coupled receptor family C group 5 member D (GPRC5D).

Data from a phase 1 clinical trial (NCT02514239) investigating the BiTE molecule AMG 420 that targets BCMA showed a response rate of 70% at the maximum-tolerated dose of 400 mg/day with 5 of 10 patients achieving a stringently defined complete response.13 Investigators are evaluating AMG 701, a BiTE molecule modified to have a longer half-life, in a successor clinical trial (NCT03287908).14

ADCs are monoclonal antibodies that target a cytotoxic cargo to MM cells. Upon binding to the target antigen, the ADC complex is internalized, and then the cytotoxic molecule is released. The ADC class of monoclonal antibodies is attractive because the agents can be safely used in patients with a high disease burden without the risk of cytokine release syndrome or neurotoxicity. Belantamab mafodotin-blml (Blenrep) is an ADC that targets BCMA and is conjugated to the microtubule poison monomethyl auristatin F. The agent was recently approved for relapsed/refractory MM based on data from the DREAMM-2 study (NCT03525678) in which it demonstrated responses in patients who had received a median of 7 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.15 Corneal keratopathy was the principal adverse effect observed. Belantamab mafodotin is administered under a risk evaluation and mitigation strategy program. Studies of the agent in combination with MM backbone drugs are ongoing.

Monoclonal antibodies have made a significant impact on the treatment landscape of MM. Current and future studies will define how best to incorporate these agents into the developing treatment strategies for patients with both newly diagnosed and relapsed MM. ■

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Bad Company: Concurrent Mutations Define Unique Subsets of NSCLC

by JANE DE LARTIGUE, PHD

OVER THE PAST 2 DECADES, non-small cell lung cancer (NSCLC) has become a poster child for precision oncology. The identification of oncogenic driver mutations to inform targeted therapy selection is the bedrock of clinical practice in this disease, with current estimates suggesting that more than half of patients harbor an actionable mutation.1 Yet lung cancer is a genomically complex malignancy and there is significant heterogeneity in the clinical behavior of tumors defined by the same oncogenic driver. As investigators have begun to unravel this complexity, co-occurring mutations have emerged as a potential explanation for some of the intradriver heterogeneity, particularly in patients with KRAS-mutant NSCLC, a notoriously “undruggable” subtype.2,3

The tumor suppressor gene STK11 is mutated across numerous cancer types,4 but has attracted significant attention in recent years as one of the most commonly co-mutated genes observed in KRAS-mutant NSCLC.2,3 Mutations in the STK11 gene are thought to promote metabolic rewiring in cancer cells, which not only enhances tumor growth and survival but also may be a key driver of therapeutic resistance.3,6

Mutations in another gene involved in regulating metabolic pathways, KEAP1, are closely linked to loss of liver kinase B1 (LKB1); somatic mutations in STK11 and KEAP1 commonly co-occur with each other and with KRAS mutations in NSCLC.2 Although the roles of these co-mutations as prognostic biomarkers and predictors of treatment response remain controversial,7 their presence could guide novel therapeutic options.

The glutaminase inhibitor telaglenastat (CB-839) is designed to target the metabolic rewiring common in cancer cells, including those with STK11 or KEAP1 mutations. Ongoing phase 2 trials of telaglenastat are examining its potential as a treatment for patients with NSCLC and other solid tumors with STK11 and/or KEAP1 mutations. Telaglenastat is among several novel agents being evaluated in clinical trials in biomarker-defined subsets targeted to these mutations (TABLE).

MASTER REGULATOR

Found on chromosome 19, the STK11 gene encodes LBK1, a serine/threonine kinase member of the calcium calmodulin family, which is ubiquitously expressed. LKB1 is activated via a phosphorylation-independent allosteric mechanism through the formation of a heterotrimeric complex with 2 accessory proteins, STRAD and MO25. Its activity is fine-tuned through a number of other interaction partners and posttranslational modifications that remain poorly understood.5,8,9

LKB1 is implicated in a range of cellular processes, including cell cycle control, cell polarity, and the DNA damage response, but its best characterized role is in maintaining cellular energy homeostasis through activation of AMPK and at least 12 AMPK-related kinases.5,6,9

In conditions of energy deprivation, LKB1 activates AMPK, which shifts the balance of metabolic activity away from adenine triphosphate (ATP)-consuming anabolic activities, such as lipid and protein synthesis, toward ATP-generating catabolic processes. Activated AMPK does this by phosphorylating a plethora of key proteins involved in these metabolic pathways. AMPK also directly (through phosphorylation of the Raptor component of the mTORC1 complex) and indirectly (through phosphorylation of TSC2) modulates the activity of a master

CONTINUED ON PAGE 76

### TABLE. Select Clinical Trials Targeting STK11 Mutations

<table>
<thead>
<tr>
<th>Agent (Sponsor)</th>
<th>Study description</th>
<th>Phase and trial name (ClinicalTrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaglenastat (CB-839) (Calithera Biosciences Inc)</td>
<td>In combination with pembrolizumab/chemotherapy versus pembrolizumab/chemotherapy as first-line therapy in metastatic nonsquamous NSCLC with KEAP1/NRF2 mutation</td>
<td>Phase 2 KEAPSAKE trial (NCT04265534)</td>
</tr>
<tr>
<td>Telaglenastat (CB-839) (Calithera Biosciences Inc)</td>
<td>As monotherapy in patients with metastatic solid tumors with NF1, KEAP1/NRF2, or STK11/LKB1 mutations</td>
<td>Phase 2 BeGIN trial (NCT03872427)</td>
</tr>
<tr>
<td>Talazoparib (Talzenna) (Southwest Oncology Group)</td>
<td>In combination with avelumab in patients with stage IV or recurrent nonsquamous NSCLC with STK11 mutation</td>
<td>Phase 2 LUNG-MAP treatment trial (NCT04173507).</td>
</tr>
<tr>
<td>Onatasertib (ATG-008) (Shanghai Antengene Corporation Limited)</td>
<td>As monotherapy in patients with advanced solid tumors with STK11 or NFE2L2 mutations or RICTOR amplifications</td>
<td>Phase 2 BUNCH trial (NCT04518137)</td>
</tr>
<tr>
<td>Olaparib (Lynparza) (National Cancer Institute)</td>
<td>As monotherapy in patients with advanced or metastatic urothelial cancer with mutations in DNA-repair genes, including STK11</td>
<td>Phase 2 (NCT03375307)</td>
</tr>
<tr>
<td>Sirpiglenastat (DRP-104) (Dracen Pharmaceuticals, Inc)</td>
<td>As monotherapy in patients with advanced or metastatic urothelial cancer with mutations in DNA-repair genes, including STK11</td>
<td>Phase 1/2 (NCT04471415)</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer
Clonal evolution is a root cause of treatment resistance in multiple myeloma that may ultimately result in triple-class refractory (TCR) disease. Patients are considered TCR when they are resistant to ≥1 treatment in all 3 standard-of-care classes (proteasome inhibitors, immunomodulatory agents, and anti-CD38 monoclonal antibodies).¹-⁴

Peptide-drug conjugates and antibody-drug conjugates represent a strategy designed to deliver a cytotoxic agent directly into tumor cells.⁵

regulator of cell growth, mTOR, linking cell metabolism to growth control.5,6,10

TUMOR SUPPRESSOR

STK11 was first identified more than 20 years ago when germline mutations in this tumor suppressor gene were shown to be responsible for Peutz-Jeghers syndrome,11 an inherited disorder characterized by benign gastrointestinal (GI) polyps, skin hyperpigmentation, and an increased risk of several types of cancer, including GI tract, gynecologic, breast, and lung cancers.3,8,16

With the advent of next-generation sequencing, somatic alterations in the STK11 gene have been identified in approximately 3% of cancers and several hundred different STK11 mutations have been described, although the functional relevance of many of them is not yet known.4,5 Although rare in most cancer types, STK11 alterations are notably enriched in some, such as lung adenocarcinoma, in which STK11 is the third most commonly mutated gene (approximately 30% of cases).10,12

In addition to loss-of-function mutations in the STK11 gene, other mechanisms can promote LKB1 activity. Because epigenetic events that affect LKB1 at the protein level are not often investigated, LKB1 loss may actually occur in an even greater percentage of lung cancers than is currently assumed.2,9,13

LKB1 is an unusual oncogene kinase in that the inactivation, rather than the activation, of its kinase activity drives tumorigenesis. Its role as a tumor suppressor is incompletely understood but is thought to be related to the aberrations in AMPK signaling that result from loss of LKB1, impacting cell growth and reprogramming cellular metabolism.7

Altered cell metabolism has long been recognized as a hallmark of cancer.14 Metabolic alterations in cancer include the process by which tumor cells derive energy from glucose. In normal cells, glucose is converted into pyruvate in the cytoplasm. The pyruvate is then typically transported into mitochondria, which use oxidative phosphorylation to produce energy in the form of ATP. In contrast, cancer cells instead favor using pyruvate to produce lactate through glycolysis, even when oxygen is plentiful.

This method is much less energy efficient and to compensate, cancer cells ramp up their glucose and glutamine uptake.6,15

Loss of LKB1/AMPK activity relieves the inhibition of mTORC1 by AMPK, allowing aberrant activation of mTORC1, which promotes cellular growth and tumorigenesis. In addition, downstream of mTORC1, expression of HIF1α is increased; in turn, this increases expression of the glycolytic enzymes and transporters that shift cancer cell metabolism toward aerobic glycolysis.5,6,16

Recent study results have suggested that, at least in KRAS-mutant NSCLC, the tumor-suppressive functions of LKB1 may be mediated by the AMPK-related kinases SIK1 and SIK3, rather than AMPK.17 Further, research has suggested that AMPK may play a conditional oncogenic role, in some cases actually conferring a survival advantage to cancer cells as a result of its ability to promote cell survival under conditions of stress.5,10

A UNIQUE NSCLC SUBTYPE

In lung adenocarcinomas, STK11 mutations frequently occur alongside other driver mutations. STK11 is among the most commonly co-mutated genes in patients with KRAS-mutant NSCLC. According to a recent analysis of KRAS-mutant NSCLC tumor samples, more than half had at least 1 additional mutation, and approximately 20% had a co-occurring mutation in STK11.18

STK11 co-mutations have begun to attract considerable attention in recent years as evidence has emerged that they define a unique subset of KRAS-mutant NSCLC. STK11 mutations have been shown to be associated with a more aggressive form of the disease, yielding poorer patient prognosis with significantly reduced survival.19

Furthermore, studies have shown that STK11 mutations, either alone or co-occurring with KRAS mutations, may drive resistance to immune checkpoint inhibitor (ICI) treatment of NSCLC; this has been found in patients with single STK11 mutations as well as in those harboring KRAS mutations and is thought to result from the effects of LKB1 loss on the tumor microenvironment. In several studies STK11 mutations were found to be associated with a lack of PD-L1 expression, as well as depletion of tumor-infiltrating lymphocytes and accumulation of immunosuppressive cells and cytokines, suggesting that LKB1 loss promotes an immunologically “cold” microenvironment.19-23

The prognostic and/or predictive role of STK11 mutations remains a topic of debate, as other studies have not been able to confirm these effects. This may be due to overlap between patients with concurrent alterations in the STK11 and KEAP1 genes. When a multivariate analysis was performed to tease apart the impacts of co-mutations in these 2 genes in KRAS-mutant NSCLC, the results revealed that KEAP1, not STK11, was associated with reduced overall survival and poor outcomes with ICI therapy.24

KEAP1 is part of an E3 ubiquitin ligase complex that targets the NRF2 protein for proteasomal degradation. NRF2 is a transcription factor that acts as a master regulator of the antioxidant response, activating the expression of hundreds of genes, including NFE2L224; that function to protect the cell and promote survival under conditions of oxidative stress.25

STK11 and KEAP1 or NFE2L2 are often found co-mutated with one another and/or with KRAS in lung adenocarcinomas.

FIGURE. Incidence of Co-Occurring Mutations in KRAS-Mutant NSCLC24

Next-generation sequencing of tumor samples from 550 patients with non–small cell lung cancer (NSCLC) harboring KRAS mutations showed the most frequently co-occurring mutations were in TPS3, STK11, and KEAP1/NFE2L2.


76 Vol. 22 | No. 03 | FEBRUARY 2021
Somatic alterations in **STK11** represent a bottleneck in tumors harboring *STK11* and **KEAPI** mutations; the metabolic stress created by these mutations requires enhanced antioxidant capacity that can be satisfied by **KEAPI** loss.1,26

The role of both **STK11** and **KEAPI** as potential biomarkers, particularly of response to therapy, continues to be evaluated. In the phase 1/2 KRYS TAL-1 trial (NCT03785249), the KRAS G12C inhibitor adagrasib (MRTX849) is being evaluated in cohorts of patients with pretreated KRAS G12C–mutant solid tumors. In the ongoing phase 2 portion of the study, adagrasib is administered at 600 mg twice daily.

At the 32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, KRYS TAL-1 investigators presented data from 79 patients with NSCLC (18 from phase 1/1b and 61 from phase 2). In an exploratory analysis of a subset of these patients, the objective response rate was 64% in patients with **STK11** co-mutations compared with 33% for patients with wild-type **STK11**. Meanwhile, there was no apparent trend for response rate among patients with **KEAPI** co-mutations.27,28

**THERAPEUTIC TARGET**

The identification of **STK11** mutations as common oncogenic drivers in certain cancer types has prompted efforts to therapeutically exploit these defects, particularly in patients with **KRAS**-mutant NSCLC, for whom treatments are currently limited.

Several strategies have been proposed, but evaluation of them has largely been limited to preclinical studies. Given the effects of the LKB1/AMPK pathway on mTOR, investigators have tested commercially available mTOR inhibitors in patients with **STK11** mutations, yielding mixed results.9,10 The ongoing single-arm phase 2 BUNCH basket trial (NCT04518137) is evaluating the dual TORC1/TORC2 inhibitor onatasertib (ATG-008) in patients with advanced solid tumors that harbor specific genetic alterations, including **STK11** and **KEAPI** mutations.

LKB1 also has been shown to play a role in the DNA damage response, and **STK11**-mutant cancer cells are more susceptible to drugs targeting DNA repair, such as PARP inhibitors.29 The combination of the PARP inhibitor talazoparib (Talzenna) and the ICI avelumab (Bavencio) is being evaluated in patients with **STK11**-mutant NSCLC in the LUNG-MAP treatment trial (NCT04173507). In addition, a phase 2 trial (NCT03375307) of the PARP inhibitor olaparib (Lynparza), for treating advanced or metastatic urothelial cancer is enrolling patients with DNA-repair defects, including **STK11** mutations.

Both **STK11** and **KEAPI** mutations appear to rewire the metabolism of cancer cells, including increasing their dependence upon glutamine. As a result, drugs that block glutamine production represent a promising strategy.6,16,25,30

The glutaminase inhibitor telaglenasat is being tested in combination with pembrolizumab (Keytruda) and chemotherapy as frontline therapy for patients with **KEAPI**- or **NRF2**-mutant NSCLC in the phase 2 KEAPSAKE trial (NCT04265534), in which patients are stratified according to **STK11** status. Meanwhile, the phase 2 BeGIN trial (NCT03872427) is examining telaglenasat in patients with **STK11**- or **KEAPI**/**NRF2**-mutant advanced solid tumors.

Telaglenasat also has been explored in renal cell carcinoma (RCC), although not in biomarker-specific populations. In the phase 2 CANTATA study (NCT03428217), the combination of telaglenasat plus cabozantinib (Cabometyx) was compared with cabozantinib alone in patients with advanced or metastatic RCC. The combination regimen failed to meet its primary end point of improving progression-free survival (HR, 0.94; P = .065), according to findings disclosed in January 2021 by Calithera Biosciences Inc, the company developing telaglenasat. The company is now focusing on advancing the novel therapy in the KEAPSAKE trial.31

Another drug candidate in this class, sirpigelasat (DRP-104), is a glutamine inhibitor that inhibits all known enzymes involved in glutamine metabolism, not just glutaminase.32 It was granted fast track designation for the treatment of **STK11**-, **NRF2**-, or **KEAPI**-mutant NSCLC by the FDA in October 2020.33 A first-in-human clinical trial (NCT04471415) was recently initiated to examine sirpigelasat alone and in combination with the ICI atezolizumab (Tencritig) in patients with advanced solid tumors, including **STK11**-, **NRF2**-, or **KEAPI**-mutant NSCLC.34

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UNTIL 2018, WHEN NIVOLUMAB (Opdivo) and ipilimumab (Yervoy) were approved for treatment-naïve patients with intermediate- or poor-risk metastatic renal cell carcinoma (mRCC), monotherapy with a VEGF tyrosine kinase inhibitor (TKI) was considered the frontline standard of care.1 Since that approval, the immuno-oncology (IO) landscape has expanded across mRCC risk groups, and that growth is poised to continue.

During a recent OncLive Peer Exchange®, a panel of experts in kidney cancer from the United States and France convened to discuss several important IO studies presented during the European Society for Medical Oncology (ESMO) Virtual Congress 2020, as well as several others that are under way and expected to report out over the next few years. The panelists also discussed some of the knowledge gaps that remain in managing mRCC, including a paucity of meaningful biomarkers to guide treatment decision-making, and how they sequence treatments for their patients despite these gaps.

CHECKMATE 9ER: NIVOLUMAB PLUS CABOZANTINIB
Investigators have previously reported single-agent activity of nivolumab, a PD-1 inhibitor, and cabozantinib (Cabometyx), a TKI that inhibits VEGF receptors and other kinases, and the rationale to combine the agents has provided a platform for the launch of several studies. This includes a phase 1 study (NCT02496208) sponsored by the National Cancer Institute (NCI) in which investigators examined nivolumab/cabozantinib alone and with ipilimumab.2 “A series of trials have demonstrated that combination IO–VEGF inhibition has improved outcomes for patients. That provided the rationale, and [the work at the NCI] provided the rationale for this trial [CheckMate 9ER] going into phase 3,” Rana R. McKay, MD, said. In the phase 1 NCI trial, both the doublet and triplet showed manageable toxicities, durable responses, and encouraging survival in patients with metastatic urothelial carcinomas and other genitourinary malignancies.2

CheckMate 9ER (NCT03141177) is a phase 3 trial that randomly assigned 651 treatment-naïve patients with advanced clear cell RCC across International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups 1:1 to nivolumab/cabozantinib (n = 323) or sunitinib (Sutent; n = 328).3 The primary end point was progression-free survival (PFS), and secondary end points included overall survival (OS), overall response rate (ORR), and safety.3

At a median follow-up of 18.1 months (range, 10.6-30.6), the median PFS was 16.6 months (range, 12.5-24.9) and 8.3 months with sunitinib (range, 7.0-9.7). The median OS was not reached (NR) with either treatment but showed an advantage toward nivolumab/cabozantinib. The ORR was 55.7% (95% CI, 50.1%-61.2%) with the doublet, with a complete response (CR) in 8.0% of patients, a partial response (PR) in 47.7%, and stable disease (SD) in 32.2%. Those in the sunitinib cohort had an ORR of 27.1% (95% CI, 22.4%-31.9%).
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22.4%-32.3%), with a CR in 4.6%, PR in 22.6%, and SD in 42.1%. Regardless of IMDC risk status, PD-L1 expression, and bone metastases, the ORR favored nivolumab/cabozantinib over sunitinib. “There was a nearly 49% reduction in the risk of progression or death, a 40% decrease in the risk of death, and improvement in responses, [making this a] dramatically positive study,” McKay said.

McKay also said the nivolumab/cabozantinib combination was associated with good health-related quality of life (QOL), with patients reporting significant improvements from baseline in measures such as disease-related symptoms. “The patients that were enrolled on the trial were heterogeneous. Patients with favorable-risk disease, intermediate-risk disease, and poor-risk disease have a different composition at baseline, and the fact that we did not see a decrement in quality of life with the combination—that’s clinically meaningful for patients,” she said, noting that she is eager to see how these data will continue to evolve, especially because this appears to be a unique conceptually similar to the cabozantinib/nivolumab combo that we [just discussed], but it’s much earlier in its development,” Martin H. Voss, MD, said. “The data that we saw [at ESMO 2020] included mostly patients from the expansion that was pursued in a phase 2 fashion on 2 different [cabozantinib] dose levels. That’s important to keep in mind,” he said. The cabozantinib doses assessed were 40 mg orally once daily (n = 30), which was the same dose used in CheckMate 9ER, and 60 mg orally once daily (n = 30), which is the typical single-agent dose of cabozantinib. All study participants received atezolizumab 1200 mg every 3 weeks. There was no comparator arm.

“We got a very strong signal for efficacy,” Voss said. The ORR was 53% (95% CI, 41%-65%) in the cabozantinib 40-mg cohort, with 1 (3%) CR, 17 (50%) PRs, and 14 (41%) patients with SD, and it was 58% in the 60-mg cohort (95% CI, 46%-70%), with 4 (11%) CRs, 17 (47%) PRs, and 12 (33%) patients with SD.

“What was striking to me is there was a very low failure rate on this regimen, which is similar to the cabozantinib/nivolumab combination. Less than 5% of the patients,” Voss said. Although Voss said that the number of patients in the study is too small to be able to draw definitive conclusions about PFS, the results were nevertheless promising regarding this exploratory end point. Patients in the cabozantinib 40-mg cohort had a median PFS of 19.5 months (range, 11.0-NR), whereas those in the cabozantinib 60-mg cohort had a median PFS of 15.1 months (range, 8.2-22.3). When examining potential biomarkers for response, baseline PD-L1 positivity and higher levels of CD8+ T cells were associated with greater tumor lesion reduction and significantly associated with overall response.

“When you look at the waterfall plot taken from [this study], we see that the majority of patients who are put on this regimen in the first-line setting benefit. We can only speculate where this is going to go with further development, but certainly the signal is there,” Voss said.

Moderator Toni K. Choueiri, MD, noted that CheckMate 9ER and COSMIC-021 provide further evidence that selection of TKIs matters in the frontline mRCC setting.

“We all struggled with whether we should do sunitinib or pazopanib [Votrient]. Both drugs, unfortunately, failed to combine with a checkpoint inhibitor. We couldn’t move to a phase 2. There was significant disease-limiting toxicity. Sunitinib was tried, and pazopanib was to be combined with nivolumab. Pazopanib was attempted to be combined with pembrolizumab [Keytruda]. These didn’t move on, [but] drugs such as cabozantinib, axitinib [Inlyta], and...
lenvatinib [Lenvima] did make it to phase 3 trials, so that’s refreshing to know,” he said.

**PROMISING UPCOMING PHASE 3 COMBINATION TRIALS**

The panelists then discussed the mechanistic properties and rationale for several combinations being explored in patients with metastatic RCC that have the potential to reshape the frontline treatment landscape. These include lenvatinib with everolimus (Afinitor) or pembrolizumab in the CLEAR trial (NCT02811861), cabozantinib/nivolumab ipilimumab in the COSMIC-313 trial (NCT03937219), and nivolumab/ipilimumab followed by nivolumab alone or with cabozantinib in the PDIGREE trial (NCT03793160).

Of these trials, only CLEAR has thus far completed accrual.7

In the CLEAR trial, investigators are comparing lenvatinib plus everolimus or pembrolizumab with sunitinib alone.7 No findings were available at the time of the Peer Exchange, but the drugs’ manufacturers have since announced a statistically significant improvement over sunitinib in PFS, OS, and ORR with lenvatinib/pembrolizumab and in PFS and ORR with lenvatinib/everolimus, with plans to release the data at an upcoming medical meeting.10 “The big surprise will be if we go to [a PFS of] 20 months–plus and 80% response [with lenvatinib/everolimus]—that would be probably the only thing that would make me change my mind [about using this combination]. But I think it’s going to be a toxic regimen, more toxic than nivolumab/cabozantinib and pembrolizumab/axitinib,” Escudier said. However, he noted that continuing to work on biomarkers will be increasingly important to enable better treatment selection.

The panelists noted that COSMIC-313 is the only trial with a control arm using a modern regimen. In this study, the control arm is nivolumab/ipilimumab rather than sunitinib. This aspect of its study design and that it is assessing a triplet (ie, cabozantinib/nivolumab/ipilimumab) generated excitement among the panelists. “I’m still thinking that it’s going to be toxic, but toxicity is OK if we step forward in terms of activity, especially complete remission, and that’s what I want to see. I hope we will see it,” Escudier said, adding that he hopes the data will be released soon to help answer the question of whether a triplet offers the best opportunity for cure.

Unlike CLEAR and COSMIC-313, PDIGREE is a sequencing trial. “[It] gives nivolumab/ipilimumab and then transitions to cabozantinib if there is progression, where the randomization between nivolumab and cabozantinib/nivolumab happens in patients who have stable disease or partial response but not CR,” Choueiri explained.

Escudier said he did not like the study design, noting it is a “little premature…. The big question we still have—and we need a good study to answer it—is whether we should continue with PD-1 or PD-L1 blockade after first IO here,” he said. Subsequently, he said he prefers the phase 3 CONTACT-03 study (NCT04338269), which is comparing atezolizumab/cabozantinib with cabozantinib alone in patients who experience radiographic tumor progression during or after immune checkpoint inhibitor (ICI) therapy for metastatic RCC.11 “[CONTACT-03] is a first phase 3 that is going to maybe answer the question of continuing [treatment with ICIs],” he said.

**TACKLING UNANSWERED QUESTIONS IN CLINICAL PRACTICE**

The panelists also examined some of the unanswered questions in optimizing treatment for patients with advanced RCC, sharing their perspectives on when and how they use ICIs and TKIs after progression on an IO regimen. “We must be data driven,” Nizar M. Tannir, MD, FACP, said. He added that it would be irresponsible to prescribe an ICI after progression on an ICI. “We must be good stewards of our resources. Health care is so expensive, and there’s toxicity when you combine a PD-1 or a PD-L1 plus a TKI. Until CONTACT-3 shows positive data, or a subsequent phase 3 trial with pembrolizumab/lenvatinib versus lenvatinib shows positive data for the combination, I will use only a TKI,” he said.

Voss agreed with the overall sentiment but said he is more nuanced in his decision-making. “The question as to how the disease has behaved up until and through first-line therapy speaks to it because I understand that getting a second IO or TKI without the underlying phase 3 data that we need is juggling resources somewhat irresponsibly. But if someone just blew through first-line therapy, and I don’t think that patients are likely to respond to a TKI alone,” he continued, “the question then becomes, ‘Is putting them on the TKI alone out of principle a good use of resources?’ For a patient who has rapidly progressed through nivolumab/ipilimumab in the first line, for instance, I’ll absolutely put the patient on a TKI-IO combination. I understand that axitinib/pembrolizumab was not developed in that space, but we have a lot of data that say it will likely be highly active. I believe that it will be,” he said.

Escudier said that use of IO after IO is not permitted in Europe, but in the absence of better biomarkers, patients with PD-L1–positive tumors may benefit from this approach. “I would use IO-IO in such patients, and I have no doubt that such patients should be treated with IO-IO because VEGF doesn’t work very well in those patients,” he said. “Cabo has a little activity but not a lot, and axitinib has little activity. So we should use IO-IO. And probably the rest of the patients need to have a TKI, and that’s why the question would be more between pembrolizumab/axitinib and nivolumab/cabozantinib, in my opinion, at this point,” he added.

Choueiri said when he gives IO after IO, he uses nivolumab/ipilimumab and that he is especially inclined to use this combination in patients with sarcomatoid histology. “We saw a 15% response rate in a non-VEGF regimen with nivolumab/ipilimumab post IO,” he said, noting that these findings were observed in the FRACTION-RCC trial (NCT02996110).12 He asked Tannir to discuss the data from CheckMate 214 (NCT02231749) that were observed with nivolumab/ipilimumab in 60 untreated patients with advanced RCC with sarcomatoid features.13

“The ORR was [approximately] 60%, with an 18% CR rate, and the median OS was 31 months for sarcomatoid,” Tannir said. It’s something we haven’t seen before. Sunitinib for the sarcomatoid variant had a median OS of 13 months. It hasn’t changed in 2 decades of targeted therapy. Ipilimumab is, in my opinion, the drug that produces the memory T cells that provide that durability when you give IO-IO therapy,” he added.
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