SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS, 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])*

**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.

* ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.

CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Please see Important Safety Information throughout, and accompanying Brief Summary of the full Prescribing Information.
SARCLISA Is the First Anti-CD38 Antibody Studied in a Phase 3 Trial in Combination With Pd vs Pd Alone
— ICARIA-MM: A multicenter, open-label, randomized, phase 3 study —

Patients with relapsed refractory multiple myeloma who received at least 2 prior therapies, including lenalidomide and a PI (N=307)

SARCLISA + Pd
(n=154)
Pd
(n=153)

*SARCLISA 10 mg/kg was administered as an IV infusion weekly in the first cycle and every 2 weeks thereafter
*Treatment administered in 28-day cycles until disease progression or unacceptable toxicity

**Primary endpoint: PFS**
Key secondary endpoints: ORR, OS

The phase 3 ICARIA-MM trial included patients with poor prognostic factors

<table>
<thead>
<tr>
<th>Treatment history</th>
<th>Patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>93% Refractory to lenalidomide</td>
<td>36% Impaired renal function</td>
</tr>
<tr>
<td>73% Refractory to IMiD® + PI</td>
<td>20% High-risk chromosomal abnormalities</td>
</tr>
<tr>
<td>56% Received prior ASCT</td>
<td>20% ≥75 years</td>
</tr>
</tbody>
</table>

*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 time to follow-up was 11.6 months.
†SCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.
ASCT=autologous stem cell transplant; IMiD=immunomodulatory drug; IV=intravenous; M-protein=myeloma protein; 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.

Please see Important Safety Information throughout, and accompanying Brief Summary of the full Prescribing Information.
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.

Important Safety Information (cont’d)

Infusion-Related Reactions (cont’d)
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.

Please see Important Safety Information throughout, and accompanying Brief Summary of the full Prescribing Information.
SARCLISA + Pd Showed a Significant Increase in ORR

ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%). 95% CI estimated using the Clopper-Pearson method.

The median duration of response among responders was 13.3 months (95% CI: 10.6, NR) with SARCLISA + Pd vs 11.1 months (95% CI: 8.5, NR) with Pd alone.1

Median time to first response was 35 days with SARCLISA + Pd vs 58 days with Pd alone among responders!

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®).5

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.

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%).

NR=not reached.
SARCLISA® Rx Only
(isatuximab-irfc) injection, for intravenous use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE
SARCLISA 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage
- Administer pre-infusion medications (see Dosage and Administration (2.2)).
- SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur (see Warnings and Precautions (5.1)).

The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone, according to the schedule in Table 1 (see Clinical Studies (14) in the full prescribing information).

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone

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

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

SARCLISA is used in combination with pomalidomide and dexamethasone

Missed SARCLISA Doses
- If a planned dose of SARCLISA is missed, administer the dose at the next possible administration time and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.2 Recommended Premedications
- Administer the following premedications prior to SARCLISA infusion to reduce the risk 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.
- The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backdrop treatment, before SARCLISA and pomalidomide administration.
- Administer the recommended premedication agents to 15 minutes prior to starting a SARCLISA infusion.

2.3 Dose Modifications
- No dose reduction of SARCLISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematological toxicity (see Warnings and Precautions (5.2, 5.4)).
- For information on drugs given in combination with SARCLISA, see manufacturer's prescribing information.
- For other medicinal 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 discoloration prior to administration, whenever solution and container permit.
- Remove the volume of ultrastar from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, and diluent bag that is equal to the required volume of SARCLISA injection that is:
  - Withdraw the recommended primary volume of SARCLISA injection and dilute with the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to the appropriate SARCLISA concentration for infusion.
  - The infusion bag must be made of polyethylene (PE), polypropylene (PP), or polyvinyl chloride (PVC) with (di-2-ethylhexyl) phthalate (DEHP) or vinyl acetic ester (VEA).
  - Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration
- Administer the recommended infusion solution by intravenous using an intravenous tubing set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion rate should be administered for a period of time that will depend on the infusion rate (see Table 2). Prepare SARCLISA infusion solution within 48 hours when stored refrigerated (up to 10 days) (see Administration (2.1)).
- Do not administer SARCLISA infusion solution concurrently in the same intravenous line with other agents.

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Initial Rate</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL</td>
<td>25 mL/hour</td>
<td>25 mL/hour every 30 minutes</td>
</tr>
<tr>
<td>Second infusion</td>
<td>250 mL</td>
<td>50 mL/hour</td>
<td>50 mL/hour every 30 minutes</td>
</tr>
</tbody>
</table>

2.6 Contraindications
SARCLISA is contraindicated in patients with severe hypersensitivity caused by the drug or to any of its excipients (see Warnings and Precautions (5.1)).

5 Warnings and Precautions

5.1 Infusion-Related Reactions
- Infusion-related reactions have been observed in 41% of patients treated with SARCLISA (see Adverse Reactions (6.1)). All infusion-related reactions reported during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an infusion-related reaction were chills, flushing, and nausea. The most common severe signs and symptoms included hypotension and dyspnea (see Adverse Reactions (6.1)).
- To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent, dexamethasone (see Dosage and Administration (2.2)). 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 the initial infusion rate of 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, as shown in Table 2 (see Dosage and Administration (2.5)). In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA for that cycle at appropriate medical management. Permanently discontinue SARCLISA therapy if a grade 3 or higher infusion-related reaction occurs and institute appropriate medical management.

5.2 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). Felbert 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 (2%), and urinary tract (3%) (see Adverse Reactions (6.1)).
- 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 develop in patients until neutrophil count recovery to at least 10 x 10⁹/L and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

5.3 Secondary Primary Malignancies
Secondary primary malignancies were reported in 3% of patients in the ISA-Pd arm and in 0.7% of patients in the pomalidomide and dexamethasone (PD) arm and in 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. Clinical studies support the development of secondary malignancies, as per International Myeloma Working Group (IMWG) guidelines.

5.4 Laboratory Test Interferences
- Beta-Human chorionic gonadotropin (Beta-HCG) interference with blood transfusions were noted in some patients with beta-hCG monoclonal antibody (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 if maternal use could cause fetal harm, including a positive indirect antiglobulin test, blood transfusions were noted in some patients with beta-hCG monoclonal antibody (see Drug Interactions (7.1)).

6 ADVERSE REACTIONS
- The following clinically significant adverse reactions from SARCLISA were described in clinical studies and observed following SARCLISA therapy:

- Infusion-Related Reactions (see Warnings and Precautions (5.1)).
- Neutropenia (see Warnings and Precautions (5.2)).
- Secondary 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 U.S. Clinical Trials
- The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma who were treated with SARCLISA alone or in combination with pomalidomide and dexamethasone (PD) (n=152) or pomalidomide and low dose dexamethasone (PDx) (n=149) (see Clinical Studies (14) in the full prescribing information). Among patients receiving Isa-Pd, 6% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer.
- The median age of patients who received Isa-Pd was 66 years (range 36–83), 58% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 6% of patients receiving Isa-Pd. Serious adverse reactions occurred in 16% 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 ischemic stroke, 22% if patients who received Isa-Pd had pneumonia and other infections (3%)).
- Permanent discontinuation due to an adverse reaction (predose-1) 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 (12%), followed by anemia (10%), and thrombocytopenia (10%).

6.3 Non-U.S. Clinical Trials
- In the context of a phase 3 study, 2% of patients exposed to SARCLISA for 6 months or longer discontinued treatment due to an adverse event (predose-1).

7 DRUG INTERACTIONS
- There were no clinically relevant pharmacokinetic interactions observed with the combination of SARCLISA, pomalidomide, and dexamethasone.

8 PATIENT FOCUS
- For more information, please refer to the patient guide included with your SARCLISA prescription.
**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 Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Lymphoproliferation</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, anesthetic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dislocation</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Parameter (% IQR)</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades (%)</td>
<td>Grade 3 (%)</td>
<td>Grade 4 (%)</td>
</tr>
<tr>
<td>Averna</td>
<td>151 (151)</td>
<td>146 (145)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>146 (145)</td>
<td>147 (145)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>148 (145)</td>
<td>146 (145)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>142 (142)</td>
<td>143 (142)</td>
</tr>
</tbody>
</table>

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

**Interference with Serological Testing**

CD38-positive or CD38-deleted CD19+ lymphocytes are not detectable in the sera of patients treated with SARCLISA, Isa-Pd, or Pd alone. SARCLISA has no effect on the detection of oligoclonal bands in the cerebrospinal fluid.

**Antibody Detection**

No patients tested positive for anti-SARCLISA antibodies in the Isa-Pd or Pd groups. No patients tested positive for anti-isatuximab-irfc antibodies in the Isa-Pd group. 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 routine immune assay results is minimal. SARCLISA, Isa-Pd, or Pd alone has no effect on the detection of oligoclonal bands in the cerebrospinal fluid.
HOPE S. RUGO, MD, FASCO, ON
Continuing Advancements in Breast Cancer Care
Unraveling the data from the 2020 San Antonio Breast Cancer Symposium

GU Cancer SUO Conference Roundup

GI Cancer Barriers to Pancreatic Trial Enrollment Michael S. Lee, MD; and Shubham Pant, MD

Immunotherapy Targeting TIGIT: Strengthening the Immune Checkpoint Blockade Luis Paz-Ares Rodriguez, MD

Hematologic Malignancies ASH 2020

Lung Cancer Spectacular Progress in Lung Cancer Care Jennifer W. Carlisle, MD
Urology Times
Leading research and analysis.
Practical advice.

www.UrologyTimes.com
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ONCOLOGY® recently sat down with Hope S. Rugo, MD, FASCO professor of medicine and director of breast oncology and clinical trials at the University of California, San Francisco Helen Diller Comprehensive Cancer Center, to discuss some of the findings presented at this year’s SABCS.

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We’ve picked this one especially for our ONCOLOGY® readers. Go to: https://bit.ly/2IRAKnZ

CORRECTIONS: In the May 2014 “Blowing Smoke: The Lost Legacy of the 1964 Surgeon General’s Report on Smoking and Health” the ‘JAMA’ engraved ashtary, Figure 3 (page 421), was incorrectly identified as the acronym for the Journal of the American Medical Association. This acronym instead stands for Japan Air Material Area, a United States Army Air Force logistics depot that existed from 1947 to 1949.

In the December 2020 article “Recent Advances in Antibody-Drug Conjugates for Lymphoma” the trade name for durvalumab was incorrectly printed, and also assume responsibility for any claims made against the publisher arising from or related to such advertisements, advertiser and advertising agency recognize and accept that the following language appears within the publication: “All statements, including product claims, are those of the person or organization making the statement or claims. The publisher does not adopt any such statement or claims as its own, and any such statement or claim does not necessarily reflect the opinion of the publisher.”

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Encouraging Advances in Hematologic Malignancies

In this issue of ONCOLOGY®, we highlight some of the most important posters and presentations from the 2020 American Society of Hematology Annual Meeting & Exposition. With encouraging follow-up data on chimeric antigen receptor T-cell therapies in both lymphoma and multiple myeloma, and promising results for bispecific antibodies and antibody-drug conjugates, clinicians have new weapons in their arsenal—and patients with relapsed/refractory hematological malignancies have a new reason to hope for better outcomes.

You will also read a review of patient-reported outcomes (PROs) of pain and related symptoms in integrative oncology practice. With pain levels being one of the primary concerns of patients with cancer, this review summarizes the most current and validated PROs to aid integrative oncology clinicians and investigators in patient care.

Also in this issue, you will find an interview with Jennifer W. Carlisle, MD, of Emory University Winship Cancer Institute. Carlisle discusses the numerous advances made for patients with lung cancer in 2020. “2020 has been remarkable,” says Carlisle. “We’ve had 10 FDA approvals; some were [for] novel treatments, and some were [for] new uses for regimens we’ve already had for NSCLC [non-small cell lung cancer]. I think that is particularly impressive amid the [coronavirus disease 2019] pandemic.”

You’ll also read an interview with Hope S. Rugo, MD, FASCO, professor of medicine and director of Breast Oncology and Clinical Trials at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center. Rugo recaps some of the important trial data discussed at the 2020 San Antonio Breast Cancer Symposium and discusses the impact those findings will have on the future treatment of patients with breast cancer. “I think the analyses of immunotherapy in the metastatic setting are already practice changing and in the next year potentially will be practice changing [in] the neoadjuvant setting as well,” she says.

Finally, you’ll read a report from the 21st Annual Meeting of the Society of Urologic Oncology, as well as expert commentary on overcoming the barriers to clinical trials for patients with pancreatic cancer.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder of ONCOLOGY®’s parent company, MJH Life Sciences®
Despite the ongoing coronavirus disease 2019 (COVID-19) pandemic, a very exciting virtual American Society of Hematology (ASH) Meeting & Exposition took place in early December 2020. The conference featured presentations focusing on the diagnosis, treatment, and prevention of disorders affecting the blood and bone marrow, as well as the immunologic, hemostatic, and vascular systems. The meeting kicked off with a “fireside chat” with Anthony Fauci, MD, who discussed the COVID-19 pandemic in relationship to specific issues for patients with hematologic malignancy and their increased risk of COVID-19 infection. In addition, he highlighted some of the information and pathophysiology related to the increased risks of thrombosis with COVID-19 infection. Quite a number of the abstracts this year focused on disseminating information on populations with hematologic malignancy and evaluating their risks and modifications of therapy related to COVID-19.

One exciting area that investigators highlighted was the use of gene editing with clustered regularly interspaced short palindromic repeats–Cas9 for blood stem cells that were then used in an autologous blood cell transplant for patients with β-thalassemia and sickle cell disease, as well as investigational gene therapy that provided effective transduction in patients with hemophilia B. These types of gene therapies could decrease the short- and long-term effects of these debilitating diseases.

Other exciting presentations included updates with longer follow-up on previously presented studies of chimeric antigen receptor (CAR) T-cell therapies in lymphoma and multiple myeloma. Many of the responses were found to be durable with longer follow-up. In addition, other subtypes of lymphoma, such as relapsed/refractory indolent lymphoma, may benefit from the use of CAR T-cell therapy. Investigators are studying CAR T-cell therapies as part of the initial therapy protocol for patients with aggressive, high-risk non-Hodgkin lymphoma who are felt to have a very poor outcome with standard chemotherapy alone. Presenters also offered initial information about this high-risk group as well as types of dual-target CAR T-cell therapies. Off-the-shelf allogeneic CAR T cells for lymphoma and multiple myeloma treatment are also under investigation.

The meeting also included initial data on several bispecific antibodies (BiTEs; targeting GPRC5D and CD3) and BFCR4350A (targeting FcRH5 and CD3) in multiple myeloma. In addition, multiple BiTEs that typically target CD20 or CD19 and CD3 are under investigation for treatment of multiply relapsed non-Hodgkin lymphoma and have demonstrated some interesting early responses in patients with multiply NHL.

With the support of the scientific community, health care teams, and patients, new discoveries and improvements in care can continue past the difficult year of 2020. I hope we can learn how to be flexible in our oncology world, support each other, and continue to gather insights from every patient we treat.
Pancreatic cancer is the third leading cause of cancer mortality in the United States, responsible for an estimated 47,050 deaths in the year 2020. It had the lowest 5-year relative survival of any cancer type diagnosed in 2000–2015, at only 9%. More aggressive first-line and second-line systemic therapy regimens have proven to improve survival in metastatic pancreatic cancer, but median survival is still shy of 1 year. In light of this limited prognosis, consensus guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network recommend that patients be informed about and/or managed in clinical trials. However, only 4.16% of patients with pancreatic cancer ultimately enrolled in clinical trials in 2014, while enrollment in existing trials is noted to be unacceptably slow. In the October issue of ONCOLOGY®, Galvin and colleagues further highlight potential barriers to enrollment of pancreatic cancer patients in both early-phase and later-phase clinical trials.

Several domains of barriers to enrollment in clinical trials have been previously described, including structural, clinical, physician, and patient barriers. The study by Galvin and colleagues specifically sought to identify clinical patient barriers, as their patient population was composed exclusively of patients who had already been seen and established in clinic and who were being considered for clinical trials. However, prior studies showed that structural barriers, such as trial availability at a given institution for a given disease or stage, and clinical barriers were the most common barriers to enrollment in trials. A recent meta-analysis and systematic review across cancer types performed by Unger and colleagues showed that 55.6% of patients did not have a clinical trial available at their institution. Thus, to increase enrollment of patients with pancreatic cancer onto clinical trials, alleviating structural barriers is necessary and will arguably yield a greater increase in enrollment.

A recent meta-analysis and systematic review across cancer types performed by Unger and colleagues showed that 55.6% of patients did not have a clinical trial available at their institution.

These factors are particularly relevant in the era of precision medicine. While biomarker-selected therapy shows promise in pancreatic cancer, newer trial designs are needed to maximize enrollment in these rarer cohorts. Ongoing multi-arm trials in pancreatic cancer, such as PRECISION-Panc in the United Kingdom or Precision Promise in the United States (clinicaltrials.gov NCT04229004), provide a framework for both biomarker-directed and biomarker-agnostic trial arms to optimize trial enrollment.

Clinical barriers to enrollment, such as failure to meet eligibility criteria, are the second most common barrier to enrollment in oncology clinical trials, with 21.5% of patients in the meta-analysis by Unger and colleagues proving ineligible for specific clinical trials. Clinical barriers in pancreatic cancer are particularly highlighted by the study by Galvin and colleagues. While patients included in the study were deemed to be qualified to enroll in a phase 1 study, 19.2% of the patients who did not enroll in a clinical trial died or transitioned to hospice, and another 15.4% had decline in functional status or disease progression. This underscores the rapid pace of progression and clinical deterioration in patients with uncontrolled, refractory pancreatic cancer. For example, in the NAPOLI-1 trial, the difference between median progression-free survival and median overall survival was about 2 to 3 months in all arms, suggesting a postprogression survival of 3 months or less. Consequently, patients with refractory pancreatic cancer typically have a limited duration of time in which they maintain an ECOG performance status of 0 to 1, as is typically required for enrollment in a therapeutic clinical trial. This is further exacerbated by the fact that many trials exclude patients with low body mass index or hypoalbuminemia. While patient selection for clinical trials must prioritize patient safety and produce results that are interpretable, overly stringent eligibility criteria also limit patient enrollment and potential generalizability of trial results to the real-world population of patients. Consequently, ASCO and the FDA
are emphasizing careful evaluation of eligibility criteria to avoid those that are overly restrictive. Additionally, wash-out periods of no therapy prior to starting on trial treatment should not be excessively long; we feel that in trials enrolling patients with refractory pancreatic cancer, the wash-out period should optimally be less than 28 days.

Given rapid clinical deterioration in pancreatic cancer, patients understandably are less likely to enroll in clinical trials if they are concerned about prolonged wait times for a trial...

Many trials also include an inclusion criterion specifying a minimum life expectancy. However, this criterion is inherently subjective, and indeed oncologists in routine clinical practice typically overestimate patients’ life expectancy by a median of 4.4 months when patients actually had 0 to 3 months to live. Given rapid clinical deterioration in pancreatic cancer, patients understandably are less likely to enroll in clinical trials if they are concerned about prolonged wait times for a trial, as Galvin and colleagues identified. Novel phase 1 trials are designed considering these potential clinical barriers. While many of these clinical barriers are intrinsic to the natural history and prognosis of advanced pancreatic cancer, clinical trials must be designed considering these potential clinical barriers.

Finally, a range of patient barriers to enrollment affect patients’ decisions to enroll in clinical trials. Galvin and colleagues highlight a number of these barriers, including concerns about time commitment and fear of adverse effects. The American Cancer Society Cancer Action Network has issued several recommendations for overcoming barriers to patient enrollment, incorporating multiple domains of barriers. While these recommendations are applicable across all cancer types, given the challenges noted in enrollment in patients with pancreatic cancer, it is particularly important to address these barriers and ensure that eligibility criteria are modernized to avoid unnecessarily restricting enrollment and to allow for timely enrollment onto appropriate clinical trials before clinical deterioration.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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16. Lee is assistant professor, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center.
17. Pant is associate professor, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center.
Enzalutamide treatment presented a clinically meaningful 27% lower risk of death than placebo for patients with nonmetastatic castration-resistant prostate cancer (CRPC), according to a presentation from the virtually held 21st Annual Meeting of the Society of Urologic Oncology.

The PROSPER trial also found that adverse events were consistent with the previously established safety profile of enzalutamide, and the overall survival (OS) rates were similar across all 3 trials that evaluated antiandrogen treatments. (PROSPER, SPARTAN, and ARAMIS). Metastases-free survival (MFS) benefits were also associated with the improved OS rates.

“All of the results from these trials support that treating patients earlier is better, and we can seriously improve OS,” Cora N. Sternberg, MD, clinical director at the Englander Institute for Precision Medicine at Weill Cornell Medicine, said in her presentation. “These trials have been reflected in the treatment recommendations from the American Urological Association, which gives strong recommendations, to use these novel hormonal agents in the nonmetastatic CRPC setting.”

“Enzalutamide treatment resulted in a 71% lower risk of radiographic progression or death when compared with placebo (HR, 0.29; 95% CI, 0.24-0.35). Moreover, MFS increased by 22.0 months with enzalutamide, to 36.6 months from 14.7 months with placebo. For MFS, median follow-up for the enzalutamide group was 18.5 months while the placebo group saw a median follow-up of 15.1 months.

A statistically significant association emerged between enzalutamide and OS, with a 27% reduction in the risk of death for patients in the enzalutamide group compared with those on placebo. Median survival for the enzalutamide group was 67.0 months compared with 56.3 months for placebo (HR, 0.73; 95% CI, 0.61-0.89). For OS, median follow-up was approximately 48 months.

The primary end point of the research was MFS, with secondary end points of OS, time to prostate-specific antigen (PSA) progression, safety, PSA response, and quality of life.

“This survival difference was present even though 84% of patients from the placebo group received at least 1 subsequent antineoplastic therapy after the study was unblinded,” explained Sternberg. “This includes the 87 patients who received enzalutamide during the open-label extension.”

Regarding MFS, the data found that enzalutamide treatment resulted in a 71% lower risk of radiographic progression or death when compared with placebo (HR, 0.29; 95% CI, 0.24-0.35). Moreover, MFS increased by 22.0 months with enzalutamide, to 36.6 months from 14.7 months with placebo. For MFS, median follow-up for the enzalutamide group was 18.5 months while the placebo group saw a median follow-up of 15.1 months.

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The PROSPER trial enrolled 1401 men with nonmetastatic CRPC defined by bone and CT scans. They were randomized 2:1 to receive either enzalutamide plus androgen deprivation therapy (n = 933) or placebo plus androgen deprivation therapy (n = 468).

The researchers noted that starting treatment earlier for these patients could improve survival rates. New standards of care are emerging in the nonmetastatic CRPC space, they explained.

“We know that in studies with enzalutamide, abiraterone (Zytiga), and apalutamide (Erleada), giving treatment earlier to these patients improves OS,” said Sternberg. “For patients who are asymptomatic, we believe that the time to delay and time to metastases, the time to symptoms and time to chemotherapy is also beneficial.”

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

REFERENCE
The 2020 San Antonio Breast Cancer Symposium (SABCS), held virtually December 8-12, highlighted new and updated findings from some of the most important clinical trials for treatments of patients with breast cancer.

ONCOLOGY® recently sat down with Hope S. Rugo, MD, FASCO professor of medicine and director of breast oncology and clinical trials at the University of California, San Francisco Helen Diller Comprehensive Cancer Center, to discuss some of the data presented at this year’s SABCS and their implications for the future treatment of patients with breast cancer.

Q: You were the lead author for the BYLieve trial looking at the combination of alpelisib and fulvestrant for patients with PIK3CA-mutated, hormone receptor (HR)-positive, HER2-negative, advanced breast cancer. Can you tell us about the updated findings coming out of that trial?

RUGO: Although it is a nonrandomized phase 2 trial, I believe this is a really important one. It has 3 cohorts, and it was designed to address the lack of prior CDK4/6 inhibitor treatment in the majority of patients who were enrolled in SOLAR-1, the trial that led to approval of alpelisib (Piqray) plus fulvestrant (Faslodex) in patients with PIK3CA-mutated, HR-positive, advanced breast cancer. BYLieve was designed to include patients in the first 2 cohorts—cohorts A and B—who had had CDK4/6 inhibitor and endocrine therapy as their immediate prior treatment. At the 2020 American Society of Clinical Oncology meeting, we presented the data from patients who had progressed on an aromatase inhibitor and CDK4/6 inhibitor and were treated with fulvestrant and alpelisib, the SOLAR-1–like regimen. [The regimen] showed efficacy in this group when compared with a real-world population as well. In cohort B, patients had their immediate prior treatment with the CDK4/6 inhibitor and fulvestrant, and they received alpelisib and letrozole. In this cohort, the majority of patients had previously been exposed to an aromatase inhibitor and had had progression on that treatment. So, this is really the most endocrine-resistant population that has been treated with alpelisib combined with endocrine therapy. All patients who were analyzed for efficacy had centrally confirmed PIK3CA mutations. The end point was the proportion of patients alive without disease progression at 6 months, assessed locally. This was 46.1% [of patients], [who all met] the criteria for efficacy. We also looked at median progression-free survival (PFS), which was 5.7 months. I think this is quite impressive, although it’s shorter than what we saw in SOLAR-1 or in cohort A of BYLieve, a less endocrine-resistant population. It’s still [a] very long [period of time] for a patient population who already have disease that is resistant to an aromatase inhibitor and are again being treated with an aromatase inhibitor. The toxicity continues to be as expected; a little improvement [occurred] over time as investigators became more comfortable using alpelisib and understood how to prevent the rash, manage the rash, and treat hyperglycemia.

Q: The SOLAR-1 study also had some biomarker analysis. Could you highlight these data and give some thoughts on those findings?

RUGO: This presentation is a bit complex. It’s looking at what happened in patients who were in the SOLAR-1 study who had...
PIK3CA alterations detected in plasma circulating tumor DNA (ctDNA). In addition, in this analysis, some data looked at next-generation sequencing (NGS). I think what’s important about this is that we use ctDNA generally as polymerase chain reaction (PCR). We don’t use NGS. It’s important to keep in mind that we’re not recommending a different type of analysis for PIK3CA mutations, as we already have an FDA approved approach, but the data that were presented demonstrated clinical benefit of alpelisib and fulvestrant in patients who had PIK3CA alterations in plasma ctDNA detected by NGS. If you looked at the group of patients who had an alteration by NGS, but it was not detectable by PCR, we didn’t see a benefit. However, the numbers of patients here are very, very small, so you can’t really interpret that information. We’re often asked if it matters whether patients have single or multiple alterations; these findings were consistent, regardless of single or multiple alterations, and [they were consistent] in patients with alterations in axons 9 and 20, which are what we looked at in SOLAR-1 for the approval and efficacy data. It doesn’t represent the nonaltered PIK3CA enrolled in SOLAR-1, because some patients without alterations in ctDNA had alterations in tissue PIK3CA. I think that it may have to do with low allele frequency or variable DNA shedding rates. For that reason, if patients have had blood tested first, and do not have evidence of a mutation, it’s important to test tumor tissue, if you can.

Many questions asked at the time of the presentation had to do with whether or not you should only test in a more recent tissue sample or [whether you should test both a recent and a] previous tissue sample. I think you should use the most recent tissue sample you have available, whatever [it is], because sometimes you don’t have the ability to biopsy a tumor in real time. PIK3CA mutations tend to be conserved over time. A slow acquisition of additional alterations occurs during the progression of metastatic disease, but you’re pretty good even looking at archival tumor tissue. So, all of this is consistent with the overall data already presented for SOLAR-1, but it gives us additional insight into ways of looking at PIK3CA alterations in tumor tissue by NGS and PCR, as well as looking at ctDNA. The data are very interesting. They shouldn’t change the way we test now, but they do provide some evidence for further evaluations in the future, as well as understanding the interrelationship between ctDNA and tissue analyses.

Q: You presented on some additional efficacy end points from the KEYNOTE-355 trial. This study was the basis for the approval of pembrolizumab (Keytruda) in the first-line setting for locally or locally recurrent unresectable or metastatic triple-negative breast cancer. What are some of the top-line data from this study?

RUGO: This very interesting study randomized patients who had developed metastatic disease within 6 months or longer after they received their last therapy in the curative setting. We looked at the different PFS and response rates based on the chemotherapy agents being used and it’s important to keep in mind that we weren’t powered to look at differences among chemotherapy agents, but we could look at forest plots and hazard ratios with the various chemotherapy agents used. If we focus on the group of patients with a combined positive score (CPS) of 10 or more for PD-L1 positivity, we see that all patients benefit from the addition of pembrolizumab regardless of the chemotherapy regimen. A total of 99 patients received nab-paclitaxel (Abraxane), 44 received paclitaxel, and 180 received gemcitabine and carboplatin. In that group, the hazard ratios were 0.57 for nab-paclitaxel, 0.34 for paclitaxel, and 0.77 for gemcitabine/carboplatin. Of note, the patients who receive gemcitabine/carboplatin tend to be patients who have relapsed earlier and already have resistance to taxane chemotherapy. We saw in the earlier presentation by Javier Cortez, as well as in the publication, that when you look at the overall forest plot, [you see] that patients with de novo metastatic disease or longer disease-free intervals tend to have a better outcome in terms of PFS. And that’s as you would expect: Those are known prognostic criteria. Of course, we were looking at checkpoint inhibitors. We also looked at overall response rates and duration of response; these too were longer in patients who received pembrolizumab vs patients who received placebo. If you looked at this by chemotherapy, all patients had an improved response by individual chemotherapy regimen if they received pembrolizumab, [and it was] particularly evident in the patients who had a CPS of 10 or more, although you certainly can see improvements in the population of those with a CPS of 1 or more as well. We looked at duration of response (DOR), and here as well we really see a remarkable difference: Among the patients with PD-L1 CPS of 10 or more, those who received placebo had a median DOR of 7.3 months, which went to 19.3 months with pembrolizumab. The bottom line is that these data led to the FDA granting accelerated approval of pembrolizumab combined with chemotherapy—either nab-paclitaxel, paclitaxel, or gemcitabine carboplatin—in November 2020 for patients who have PD-L1-positive disease, defined as a CPS of 10 or more. We did see enrichment of PFS and response in patients who had higher PD-L1-positive disease; we saw this remarkable DOR as well as an improvement in overall response.

Q: The regimen of oral paclitaxel and encequidar was getting a lot of attention and interest at the meeting. From your perspective, how does the addition of encequidar improve the poor bioavailability of oral paclitaxel alone? Also, if this regimen is granted FDA approval, what will
be the importance of this oral option for patients with metastatic breast cancer?

**RUGO:** These are really important questions. First, encequidar is a very well tolerated agent that doesn’t cause any toxicity, but oral taxanes are just not well absorbed. So [the mechanism of action] is really thought to be due primarily to P-glycoprotein pumping out the drug as soon as it gets to the cell. Using encequidar allowed very good absorption of oral paclitaxel. It’s actually been surprisingly easy for our patients to manage this in our neoadjuvant experience. Now, they fast overnight, they take the encequidar, they wait 30 to 60 minutes, they take the oral paclitaxel, and then they fast a little bit longer. They can drink tea, water, or coffee without milk during that time period, and then they eat after that. And it’s actually worked out really well. I was kind of worried about the fasting, but it’s not an issue. In addition, because the nausea can be very well controlled, it hasn’t been an issue for patients taking this 3 days in a row weekly. This would offer an option for patients to not need that IV access, which is so challenging in breast cancer patients using the veins in the arm. Also, just not having to come into the infusion center every week also is a tremendous benefit for patients; they could come in every 3 weeks [as was standard] when we were giving IV paclitaxel every 3 weeks in the early days.

The other thing to mention is neuropathy—a big issue for me. If my patients have neuropathy, it affects everything they do. If we can reduce the neuropathy, with efficacy equal to that of other treatments, even if you had a drug that was given IV weekly, it would be super. If the oral paclitaxel plus encequidar leads to a reduced incidence of neuropathy—lower grade and a delayed onset—this would allow us to treat patients much more easily with a taxane with good efficacy in the metastatic setting.

**Q:** What studies would you consider the most practice-changing or transformative over the last year?

**RUGO:** I think the analyses of immunotherapy in the metastatic setting are already practice-changing, and in the next year they potentially will be practice-changing in the neoadjuvant setting as well. We have really cool anti-body-drug conjugates, trastuzumab deruxtecan (Enhertu) and sacituzumab govitecan (Trodelvy), that are changing care for HER2-positive and for triple-negative disease. We have now a very potent and less toxic oral tyrosine kinase inhibitor (TKI), tucatinib (Tucysa), which is being combined with capcitabine and trastuzumab and results in not just improved PFS but improved overall survival have the metastatic setting. In patients with active brain metastases, very exciting data have led to a whole bunch of new studies. We’ll see data in the next year about the efficacy of these antibody-drug conjugates (ADCs) in other populations, such as patients who have newly defined HER2-low disease—not HER2-positive but also not 0 by immunohistochemistry IHC. I think [some] really intriguing studies will potentially allow us to further expand the use of ADCs, a highly effective therapy. Then, we’ve seen some really amazing data using TKIs, with the cyclin-dependent kinase inhibitors in patients with HR-positive disease in the metastatic setting. At San Antonio, we saw the updated survival data for MONALEESA-7, which are very impressive in pre- and perimenopausal women. A lot of work is going on looking at additional agents that attack the PI3 kinase pathway, but we saw disappointing data about AKT inhibitors with chemotherapy in both HR-positive and triple negative disease; however, more data will come. Of course we have alpelisib with additional agents being studied in the PIK3CA-mutated population with hormone therapy, so, really, a lot is going on.

**FINANCIAL DISCLOSURE:** The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any
The addition of subcutaneous daratumumab (Darzalex) to pomalidomide (Pomalyst) and dexamethasone (Pd), in patients with relapsed/refractory multiple myeloma (RRMM) who had received 1 or more prior lines of therapy, according to results from the phase 3 APOLLO study presented at the 2020 American Society of Hematology Annual Meeting.

Moreover, the combination achieved a significantly deeper response, compared with pomalidomide monotherapy, including a higher complete response (CR) rate (25% vs 4%, respectively) and minimal residual disease (MRD) negativity (9% vs 2%).

“Daratumumab is another CD38 monoclonal antibody with multiple modes of action, which has shown not only single-agent activity, but also whenever this drug was combined with other standard regimens, either in a lab setting or in the frontline setting, there was a significant improvement in progression-free survival (PFS), and also in overall survival (OS),” Meletios A. Dimopoulos, MD, from the National and Kapodistrian University of Athens in Greece, said during a press briefing.

In the phase 1b study of intravenous D-Pd, the combination induced deep responses and appeared to be well tolerated in patients with heavily pretreated RRMM, including patients who previously received treatment with lenalidomide (Revlimid). Therefore, the FDA approved D-Pd to treat patients with RRMM with 2 or more prior lines of therapy.

Recent studies have found that the subcutaneous formulation of daratumumab is comparable with the intravenous formulation in terms of efficacy and safety. Moreover, it is associated with a statistically significant reduction in infusion-related reaction rates and has a considerably shorter administration duration (just 5 minutes, on average).

In the open-label, multicenter phase 3 APOLLO study (NCT03180736), the researchers evaluated subcutaneous daratumumab plus Pd, compared with Pd alone, in 304 patients with RRMM with 1 or more prior lines of therapy, including lenalidomide or a proteasome inhibitor.

To be eligible for the trial, patients with only 1 prior line of therapy were required to be refractory to lenalidomide. Prior treatment with anti-CD38 or pomalidomide was not permitted.

All patients received 28-day treatment cycles until progressive disease or unacceptable toxicity. Patients were randomized 1:1 to received D-Pd (n = 151) or Pd alone (n = 153). The D-Pd regimen consisted of 1800 mg subcutaneous daratumumab every week for cycles 1-2, every other week for cycles 3-6, and every 4 weeks for cycles 7 on; 4 mg pomalidomide on days 1-21; and 40 mg dexamethasone on days 1, 8, 15, and 22. Median duration of subcutaneous administration was 5 minutes (range, 1-22).

Posttreatment follow-up was conducted every 4 weeks for patients who discontinued treatment. Survival follow-up was conducted every 12 weeks following progressive disease or the start of subsequent therapy.

PFS served as the primary end point. Secondary end points included overall response rate (ORR), rates of very good partial response (VGPR) or better and CR or better, MRD negativity rate, OS, time to response, duration of response, time to next therapy, and safety.

The majority of patients had International Staging System stage I (45%) disease, their median age was 67 years (range, 35-90), and 35% had cytogenetic risk (presence of del17p, t[14;16], or t[4;14]). Eleven percent of patients had received 1 prior line of therapy (median, 2; range, 2-5). In addition, 79.6% of patients were refractory to lenalidomide, 48.0% of patients were refractory to a proteasome inhibitor, and 42.4% of patients were refractory to both. Median duration of treatment was 11.5 months with D-Pd, compared with 6.6 months with Pd.

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Treatment with axicabtagene ciloleucel (axi-cel; Yescarta) induced high rates of durable responses in patients with indolent non-Hodgkin lymphoma (NHL), according to extended follow-up results of the ZUMA-5 trial that were presented during the 2020 American Society of Hematology Annual Meeting.1

Results showed that, at a median follow-up of 17.5 months, the objective response rate (ORR) by independent radiology review committee (IRRC) was 92% (95% CI, 85%-97%) and the complete response (CR) rate was 76% (95% CI, 67%-84%). The partial response (PR) rate was 16%; the stable disease (SD) rate was 3%, and 5% of patients were undefined.

In patients with follicular lymphoma, the ORR was 94%, with a CR rate of 80% and a PR rate of 14%. Four percent of patients had SD and 2% were undefined. In those with marginal zone lymphoma (MZL), the ORR was 85%, with a CR rate of 60% and a PR rate of 25%; 0 patients had SD and 15% of patients were undefined.

“Axicel may be a highly promising therapeutic approach for patients with relapsed/refractory indolent NHL,” said lead study author Caron A. Jacobson, MD, MMSc, a senior physician and medical director of the Immune Effector Cell Therapy Program, Dana-Farber Cancer Institute, and an assistant professor of medicine at Harvard Medical School. “Given the long natural history of these diseases, safety is of paramount importance. The safety profile was manageable and reversible and appeared to be at least similar to that of axi-cel in aggressive lymphomas. This may have implications for the possibility of outpatient therapy, and evaluation of this is planned.”

Patients with advanced-stage indolent NHL, including follicular lymphoma and MZL, frequently relapse on standard treatment; remission durations for these patients shorten with subsequent lines of therapy.

Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that is currently approved for the treatment of adult patients with relapsed/refractory large B-cell lymphoma following 2 or more lines of systemic treatment. The regulatory decision was based on findings from the ZUMA-1 trial, in which axi-cel elicited an ORR of 82% in the modified intent-to-treat population, along with a 58% CR rate.2

In the multicenter, single-arm, phase 2 ZUMA-5 trial (NCT03105336), investigators sought to evaluate axi-cel in 151 patients with relapsed/refractory indolent NHL, either follicular lymphoma or MZL, following 2 or more lines of therapy. Five patients could not be treated due to transformation to diffuse large B-cell lymphoma (DLBCL) via pretreatment biopsy (n = 1), ineligibility (n = 3), and death prior to infusion (n = 1). Therefore, a total of 146 patients with follicular lymphoma (n = 124) or MZL (n = 22) were treated as of the data cutoff.

To be eligible for enrollment, patients needed to have relapsed/refractory follicular lymphoma of grades 1 to 3A or MZL that was nodal or extranodal. Patients must have received 2 or more prior lines of treatment that included an anti-CD20 monoclonal antibody plus an alkylating agent.3

Conditioning regimens included 30 mg/m2 of intravenous (IV) fludarabine and 500 mg/m2 of IV cyclophosphamide on days –5, –4, and –3. Axi-cel was administered at 2 x 106 CAR T cells/kg.4 The primary end point of the trial was ORR, which was IRRC-assessed per Lugano classification. Secondary end points included IRRC-assessed CR rate, investigator-assessed ORR, duration of response (DOR), progression-free survival (PFS), overall survival (OS), adverse effects (AEs), and CAR T-cell toxicity.
and cytokine levels. The MZL cohort was exploratory, and all analyses for this cohort were descriptive in nature, Jacobson noted.

The efficacy analyses included 104 patients: those with follicular lymphoma who had at least 1 year of follow-up (n = 84), and patients with MZL with at least 4 weeks of follow-up (n = 20). The safety analysis included all 146 treated patients.

As of March 12, 2020, median follow-up for the efficacy analysis was 17.5 months (range, 1.4-31.6). Median follow-up for the safety analysis was 15.1 months (range, 0.5-31.6). Axi-cel was manufactured for all 151 enrolled patients and was delivered to the study site a median of 17 days following leukapheresis.

Overall, patients’ median age was 61 years (range, 34-79); 35% were 65 years or older. Fifty-seven patients were male, and 38% had an ECOG performance status of 1. Most patients (86%) had stage III to IV disease, but less than half (47%) had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 3 or lower, and 49% had high tumor bulk based on Groupe d’Etude des Lymphomes Folliculaires criteria.

Median number of prior therapies was 3 (range, 1-10), but 64% received 3 or more treatments; 29% had previously received a PI3K inhibitor. Sixty-eight percent of patients had refractory disease, and 55% had disease progression for more than 2 years from their first therapy containing anti-CD20 monoclonal antibodies. Twenty-three percent of patients had undergone prior stem cell transplantation.

Results also showed that median time to first response was 1 month (range, 0.8-3.1). Additionally, of 25 patients with follicular lymphoma who initially achieved a PR, 52% subsequently converted to a CR after a median 2.2 months (range, 1.9-11.2).

The response rate was consistent across key subgroups analyzed on the study, including age, sex, ECOG performance status, FLIPI score, high tumor burden, number of prior therapies, prior PI3K inhibition, prior autologous stem cell transplant, relapsed/refractory disease, progression of follicular lymphoma within 24 months from initiating first anti-CD20 monoclonal antibody-containing therapy, CD19 status, and corticosteroid and/or tocilizumab (Actemra) use.

At a median follow-up of 17.5 months, the estimated median DOR was not reached in the overall population, and the 12-month DOR rate was 71.7% (95% CI, 60.7%-80.1%).

In the follicular lymphoma cohort, which had a median follow-up of 12.1 months, the median DOR was not estimable (NE) and the 1-year DOR rate was 77%. Moreover, 64% of patients with follicular lymphoma had an ongoing response at data cutoff. Additionally, responses were ongoing in 78% of patients who achieved a CR and in 17% of patients with a PR.

In the MZL cohort, the median DOR was 10.6 months and the 1-year DOR rate was NE.

When the median DOR was calculated by best response, patients with follicular lymphoma who had either a CR or PR had a median DOR of NE and 2.8 months, respectively; 1-year DOR rates were 87.0% and 13.6%, respectively.

In the patients with MZL who achieved CR or PR, median DOR was 10.6 months and 8.1 months, respectively; the 1-year DOR rates were NE and 0%, respectively. However, Jacobson noted that the follow-up for the MZL cohort is much more limited, making these DOR data immature.

Moreover, further findings showed that median PFS was NE (95% CI, 23.5-NE), and the 1-year PFS rate was 73.7%. In patients with follicular lymphoma, median PFS was NE and the 12-month PFS rate was 77.5%; in patients with MZL, median PFS was 11.8 months and the 1-year PFS rate was 45.1%.

Median OS in all patients was NE; the 1-year OS rate was 92.9%. Median OS was NE and the 1-year OS rate was 92.8% in patients with follicular lymphoma; in patients with MZL, median OS was NE and the 1-year OS rate was 92.9%.

Regarding safety, grade 3 or higher AEs occurred in 86% of patients, the most common of which were cytopenias (70%) and infections (16%). Three deaths were reported: 1 was related to axi-cel due to multisystem organ failure in the context of cytokine release syndrome (CRS; day 7), while the other 2 were unrelated to study treatment and were, respectively, due to aortic dissection (day 399) and coccidioidomycosis (day 327).

Overall, 82% of patients experienced any-grade CRS, and 7% had grade 3 or higher CRS. Ninety-six percent of patients experienced pyrexia and 41% had hypotension. Moreover, approximately half (49%) had their AEs managed with tocilizumab and 17% received corticosteroids. Grade 4/5 CRS occurred in 1 patient each, and no patients had ongoing CRS as of the cutoff date.

Median time to onset of CRS was 4 days (range, 1-15) and median duration of events was 6 days (range, 1-27). Ninety-nine percent of patients, however, had resolved events.

The overall incidence of any-grade and grade 3 and higher neurologic AEs were 60% and 19%, respectively. Tremor and confusional state occurred in 52% and 40% of patients, respectively. To manage this AE, 36% of patients received corticosteroids and 6% were given tocilizumab. Median time to onset of neurologic events was 7 days, and median duration of events was 14 days. Ninety-three percent of patients had resolved events.

When stratified by cohort, patients with MZL had higher rates of grade 3 or higher neurologic events vs those with follicular lymphoma, at 41% vs 15%, respectively.

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Grade 4 neurologic events occurred in 3 patients; no grade 5 events were reported. At data cutoff, events were ongoing in 6 patients, which included grade 1 memory impairment (n = 2); grade 1 attention disturbance, intermittent paresthesia, and tremor (n = 1 for each); and grade 2 facial paresthesia (n = 1).

Furthermore, median time to peak of anti-CD19 CAR T-cell levels after the infusion of axi-cel was 9 days (range, 8-371). The CAR T-cell expansion by peak and area under the curve trended higher in patients with MZL. Seventy-eight percent of patients with evaluable samples had low levels of detectable CAR gene-marked cells at 1 year.

A trend toward higher CAR T-cell levels was seen in patients with follicular lymphoma who had an ongoing response at 12 months, Jacobson added. Moreover, peak CAR T-cell levels were associated with grade 3 or higher CRS and neurologic events in patients with FL. Similar trends linked between CAR T-cell expansion and outcomes were seen in patients with MZL.

In an interim analysis of ZUMA-5, in which 96 patients were evaluable for efficacy, the ORR was 93% (95% CI, 86%-97%) and the CR rate was 80% (95% CI, 71%-88%); median time to first response was 1 month (range, 0.8-3.1). In patients with follicular lymphoma (n = 80), the ORR was 95% and the CR rate was 81%. In those with MZL (n = 16), the ORR was 81% and the CR rate was 75%.

In a press briefing during the meeting, Jacobson suggested that the biology of indolent NHL could be a reason for the higher efficacy rates and more tolerable safety profile with axi-cel compared with data in more aggressive lymphoma subtypes.

“It is the disease biology itself; we know that each of these lymphomas have unique microenvironments that may or may not make them more susceptible to immunologic killing,” Jacobson explained. “We know follicular lymphoma is a disease that can be cured by allogeneic stem cell transplant to a larger degree than what is seen with aggressive B-cell non-Hodgkin lymphomas. That may, in part, explain the efficacy.”

Additionally, Jacobson noted that the patients with MZL had slightly worse toxicity, similar to patients with DLBCL.

“Theyir pretreatment inflammatory markers were elevated, similar to DLBCL,” said Jacobson. “I think the disease itself is probably what dictates the toxicity profiles that we’re seeing.”

Press briefing moderator Catherine Bollard, MD, MChB, of the Children’s National Research Institute—where she is both director of the Center for Cancer and immunology director of the Program for Cell Enhancement and Technologies for Immunotherapy—commented on the longer ZUMA-5 findings.

“The work of Dr Jacobson and colleagues is really very laudable. The longer the follow-up, the more robust the data, [and we will then] really be able to draw some very effective comparisons, [more so] than with historic [progression-free survival] and [disease-free survival] data, which will only really happen with the test of time,” said Bollard. “It’s really exciting to see these data in the [indolent] lymphoma setting, and I actually would like to see [this treatment] moved further up for the treatment of patients earlier in their disease process.”

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Higher doses of the telomerase inhibitor imetelstat improved overall survival (OS), spleen response, and symptom response in patients with myelofibrosis who are relapsed after or refractory to therapy with Janus kinase (JAK) inhibitors, according to an analysis of the phase 2 IMbark study (MYF2001; NCT02426086) presented at the 2020 American Society of Hematology (ASH) Annual Meeting and Exposition.\(^1\)

The randomized, single-blind study evaluated the efficacy of 2 doses of intravenous imetelstat—4.7 mg/kg and 9.4 mg/kg, both every 3 weeks—and found dose-related clinical benefits in symptom response and OS in the higher-dose arm.

The dose-related improvement in OS in the higher-dose arm was further supported by analyses of IMbark with closely matched real-world controls.\(^2\)

The intent-to-treat (ITT) analysis presented at ASH specifically evaluated the association between OS and spleen response, symptom response, and fibrosis improvement, and set out to explore the effects of prognostic pretreatment baseline characteristic factors on survival.

The co-primary end points of spleen response and symptom response rates were measured by spleen volume reduction of 35% or more and a total symptom score reduction of 50% or more at week 24. OS was a key secondary end point, and analysis of OS was performed based on a database lock in April 2020; median follow-up was 41.7 months (range, 0.2-49.2). All 107 enrolled patients (n = 59 in 9.4 mg/kg arm; n = 48 in 4.7 mg/kg arm) were included in the ITT analysis.

As of February 2020, median OS was 28.1 months in the 9.4 mg/kg arm (95% CI, 22.8-31.6) and 19.9 months in the 4.7 mg/kg arm (95% CI, 17.1-33.9). Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg. At 24 months, 57.9% of patients were alive in the high-dose arm, compared with 42% in the low-dose arm.

Lower risk of death was also found to significantly correlate with improved bone marrow fibrosis in the high-dose arm.

Patients who achieved symptom response also exhibited a trend of longer OS compared with patients who did not achieve symptom response or who had no assessment (HR, 0.79; 95% CI, 0.41-1.51). Of patients in the high-dose arm, 32% had a total symptom score reduction of 50% or more, compared with 6.3% of those in the low-dose arm. A similar trend was seen for patients who achieved spleen response at week 24 (HR, 0.46; 95% CI, 0.11-1.92).

Of the 57 patients with available bone marrow data, 19 (33.0%) had 1 degree of bone marrow fibrosis improvement or greater, and they had significantly longer OS than those who had worsening bone marrow fibrosis (HR, 0.36; 95% CI, 0.13-0.96; P = .04). Irrespective of treatment dose, investigators identified several baseline disease characteristic factors as prognostic for survival. Pretreatment categorization as high risk (by Dynamic International Prognostic Scoring System), ECOG performance status, transfusion dependency, higher baseline neutrophils, and lower baseline hemoglobin and platelet values all correlated with an increased risk of death, according to the investigators.\(^\ast\)

**REFERENCES**


Continued Ibrutinib Treatment vs Placebo: Similar 1-Year DFS in CLL/SLL

Ryan McDonald

Continued treatment with ibrutinib (Imbruvica) or placebo induced similar 1-year disease-free survival (DFS) following a fixed-treatment duration of ibrutinib and venetoclax (Venclexta) in patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), following confirmed undetectable minimal residual disease (MRD), according to data presented at the 2020 American Society of Hematology Annual Meeting and Exposition.1

The results support fixed-duration treatment of ibrutinib and venetoclax in this patient population.

The primary goal of the study was to compare 1-year DFS between the continued administration of ibrutinib or a switch to placebo in patients who achieved a confirmed undetectable MRD, which was defined as undetectable serially over 3 or more cycles of therapy, and unnoticeable in peripheral blood and bone marrow.

The CAPTIVATE trial is a multicenter, international phase 2 study of first-line ibrutinib and venetoclax across 2 cohorts: one involving MRD and the other fixed duration. In this cohort, patients received 3 cycles of ibrutinib followed by 12 cycles of the combination. Patients were then randomized to receive placebo or further ibrutinib treatment depending on their MRD status.

Among 149 evaluable patients (median age, 58 years; range, 28-69), 58% achieved confirmed undetectable MRD and were randomized to either continued ibrutinib alone (n = 43) or placebo (n = 43). The remaining 63 patients who did not reach confirmed undetectable MRD were randomized to continue receiving ibrutinib (n = 31) or the combination (n = 32).

Results showed that continued ibrutinib following a confirmed undetectable MRD resulted in a 1-year DFS of 100% compared with 95.3% in the placebo group (P = .1475).

After a median follow-up of 31.3 months, all evaluable patients achieved a 30-month progression-free survival (PFS) of 95.3% (95% CI, 90.4%-97.8%). Each randomized arm in both the confirmed undetectable MRD and unconfirmed undetectable MRD group achieved a 30-month PFS of 95% or greater.

Increases in undetectable MRD were greater with continued combination therapy compared with ibrutinib alone in patients who had unconfirmed undetectable MRD following the 12 cycles of the combination. Following additional randomized treatment with ibrutinib, undetectable MRD in bone marrow increased from 32% to 42% in those who received ibrutinib alone, compared with an increase from 31% to 66% in patients who continued to receive the combination. Moreover, undetectable MRD in peripheral blood remained at 45% for patients who received additional ibrutinib and increased from 50% to 69% in patients who received the combination.

In the group with confirmed undetectable MRD, 4 patients experienced adverse events (AEs) that led to dose reduction after randomization. Four patients in the unconfirmed undetectable MRD group—2 each for ibrutinib alone and the combination—experienced AEs that led to dose reduction after randomization. There were no treatment discontinuations as a result of AEs in the confirmed undetectable MRD group compared with 3 (1 for ibrutinib alone and 2 for the combination treatment) in the group with unconfirmed undetectable MRD.

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

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

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


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With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.¹

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

Selinexor (Xpovio) demonstrated a clinical benefit in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) across age groups, according to results of a post hoc analysis of the SADAL trial that were presented during the 2020 American Society of Hematology (ASH) Annual Meeting.1

Findings showed that there was no statistical difference in objective response rate (ORR) in patients aged younger than 65 years (n = 52) vs those 65 years and older (n = 82), at 36.5% and 24.4%, respectively (P = .189). The complete response (CR) rates were 17.3% and 11.0%, respectively (P = .431); the partial response (PR) rates were 19.2% in younger patients vs 13.4% in older patients.

The median duration of response (DOR) was 9.7 months in patients aged younger than 65 years compared with 9.2 months in those 65 years and older. Moreover, the incidence of treatment-related adverse events (TRAEs) was similar between the 2 age groups.

“Selinexor is an active, convenient, oral option for patients with relapsed DLBCL, including older patients,” lead study author Marie Maerevoet, MD, of the Department of Hematology at Institut Jules Bordet in Brussels, Belgium, said in a virtual poster presentation during the meeting.

Selinexor is a first-in-class, oral selective inhibitor of nuclear export; it reactivates tumor suppressor proteins, binding to and inactivating XPO1. In June 2020, the FDA approved selinexor for the treatment of patients with relapsed/refractory DLBCL, or de novo or transformed follicular lymphoma, after 2 or more prior therapies, based on earlier findings from the SADAL study.2

In the multicenter, open-label, phase 2b SADAL study, investigators evaluated twice-weekly 60-mg selinexor monotherapy administered in 28-day cycles in this patient population until disease progression or unacceptable toxicity. The study was initially designed to evaluate selinexor at a 100-mg twice-weekly dose, but this dosage was discontinued in the study protocol in March 2017.3

Eligible patients had received at least 2 prior treatments, and had pathologically confirmed de novo DLBCL, or DLBCL transformed from indolent lymphoma.

A total of 134 patients were enrolled. The primary end point was ORR, which was independently assessed by a central imaging committee; secondary end points included overall survival (OS), DOR, and safety.

Patients were evenly split between good prognosis (45%) and poor prognosis (46%) by the Revised – International Prognostic Index (2% were very good and 7% were unknown).

Previously, data showed that selinexor elicited an ORR of 29% (95% CI, 22%-38%), including a CR rate of 13.3% and a 15.7% PR rate. A total of 8.2% of patients had stable disease and 62.7% had either progressive disease or were not evaluable. Overall, the median DOR was 9.3 months (95% CI, 4.9 to not estimable). The median time to at least a PR was 8.1 weeks (range, 6.7-16.4).

In the post hoc analysis presented at the 2020 ASH Annual Meeting, investigators sought to determine whether there were differences in efficacy and safety of selinexor in patients with relapsed/refractory DLBCL when stratified by age: younger than 65 years (39%) or at least 65 years (61%).

Baseline characteristics, aside from age, were similar between the 2 cohorts. In the younger group, the median age was 57 years (range, 35-64) and most patients (84.6%) were aged between 51 and 64 years. A total 61.5% of patients in this cohort were male, and 82.7% of patients had de novo DLBCL. Regarding DLBCL subtypes, patients had germinal center B (GCB; 53.8%), non-GCB (40.4%), or nonclassified disease (5.8%).

In the cohort 65 years and older, the median age was 73 years (range, 63-91) and 40.2% of patients were 75 years and older. A total of 57.3% of patients were male, and 73.2% had de novo DLBCL.
Continued from page 14

ASH-Multiple Myeloma: Addition of Subcutaneous Daratumumab to Pd Improves Clinical Benefit in RRMM

Compared with Pd alone, D-Pd demonstrated superior PFS (HR, 0.63; 95% CI, 0.47-0.85; \( P = .0018 \)), representing a 37% reduction in the risk for progression or death. Median PFS was 12.4 months for patients treated with D-Pd, compared with 6.9 months in patients treated with Pd alone. Moreover, D-Pd achieved longer PFS in patients who were previously treated with lenalidomide, compare with those who were not (9.9 vs 6.5 months).

After a median follow-up of 16.9 months, 99 patients (33%) had died. The risk for death was decreased by 9% with D-Pd (HR, 0.91; 95% CI, 0.61-1.35); however, survival data are immature and follow-up is ongoing.

Similarly, ORR was higher in the D-Pd group, compared with the Pd group (69% vs 46%; OR, 2.68; 95% CI, 1.65-4.33; \( P < .0001 \)). CR rates for the daratumumab regimen were also reported to be superior, compared with Pd alone (24.5% vs 3.9%, respectively), including VGPR rates (31.0% vs 19.6%).

The researchers also saw a 4.3-fold increase in MRD negativity with D-Pd (9% vs 2%; \( P = .0102 \)).

The safety of D-Pd was consistent with its known profile. The most common TRAEs occurring in 10% or more of either age group were comparable between the 2 arms. Overall, the most common TRAEs were thrombocytopenia, nausea, and fatigue, which can be managed by dose reductions and antiemetic supportive care, Maerevoet said.

Older patients did experience lower rates of thrombocytopenia compared with younger patients (50.0% vs 59.6%, respectively) as well as anemia (30.5% vs 36.5%), but had higher rates of asthenia (18.3% vs 11.5%), nausea (54.9% vs 46.2%), vomiting (31.7% vs 17.3%), and decreased weight (26.8% vs 13.5%), which were expected, Maerevoet said.

Selinexor is also approved by the FDA for the treatment of patients with relapsed/refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

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The coronavirus disease 2019 (COVID-19) pandemic stole the medical spotlight in 2020, and rightfully so. But what was sometimes lost in the never-ending news cycle and the coverage of the worldwide race for a vaccine was that advances in other diseases—particularly cancer—continued on.

Against the difficult and trying backdrop of the pandemic, cancer investigators persisted, and for patients with lung cancer, that persistence paid off in spectacular ways. With several new FDA approved treatments, as well as 2 new targetable mutations in non–small cell lung cancer (NSCLC), 2020 was a banner year in the overall lung cancer space.

ONCOLOGY® recently sat down with Jennifer W. Carlisle, MD, of Emory University’s Winship Cancer Institute, to discuss the many advances made during the last year for patients with lung cancer along with her hopes for further significant milestones in the year to come.

Q: How would you characterize 2020 in terms of the advancements made for patients with lung cancer?

CARLISLE: I would say 2020 has been remarkable. We’ve had 10 FDA approvals: Some were novel treatments and some were new uses for regimens we’ve already had for NSCLC. I think that is particularly impressive amidst the COVID-19 pandemic. And it’s important to note that all of these advances are the result of patients enrolling on clinical trials, including during this pandemic. We’ve learned from a lot of different registries, particularly the TERAVOLT registry, about just how high-risk our patients with lung cancer are for severe effects of COVID-19. So, the fact that we continue to make these advances amidst this global pandemic is remarkable.

Some of the TERAVOLT registry results to highlight are that our patients older than 65 years, those who have medical comorbidities, and those with an ECOG performance status of 2 or greater are all at the highest risk for COVID-19 complications, and our treatments may or may not contribute to this risk. We saw higher deaths associated with patients on chemotherapy or chemotherapy/immunotherapy but not immunotherapy alone.

Q: Of all the 2020 advancements made to treat patients with lung cancer, do any stand out as having the greatest impact?

CARLISLE: I wouldn’t say so in terms of the number of patients, but I think the biggest impact has been in adding to our nuanced understanding of lung cancer, [continuing to realize] that not all lung cancers are the same. As of late 2019, we had 5 targetable mutations—EGFR, ALK, RAS, BRAF, and NTRK—but a year later, we now have 3 new drugs approved for 2 completely new targets in NSCLC.

The first target is [composed of] the RET fusions, which we can see in 1% to 2% of patients with NSCLC, as well as some other malignancies, most commonly papillary thyroid cancer. While we’ve known about RET fusions in lung cancer for 8 years or so, the drugs that we previously had for this were repurposed multikinase inhibitors that didn’t have the best RET activity. But within the past 3 years, we’ve seen studies for 2 selective RET inhibitors, selpercatinib (Retevmo) and pralsetinib (Gavreto), and they are now FDA approved. Both agents showed good responses in patients who were treatment naive and previously treated alike, and both showed good data with respect to brain metastases, indicating good central nervous system penetration.

The second main target is [composed of] MET exon 14 skipping alterations, seen in 3% to 4% of patients with lung
cancer. This target is unique, because it’s not the typical driver pathway. MET exon 14 actually encodes a binding domain for ubiquitin-mediated degradation. When you lose this docking site, essentially you can’t recycle MET and it stays more active in the cell membrane, and this is what causes the cancer to grow. So, a study looking at capmatinib (Tabrecta) looked at patients with both MET exon 14 skipping alterations as well as MET amplifications, and [the researchers] found that specifically in the skipping alteration category, patients had a very robust response, with an objective response rate of more than 60% in the first-line setting. Learning about these 2 new targets, bringing the total to 7, has moved the lung cancer field along. And, [knowing about] these 7 alterations reinforces the need to do multiplex testing, ideally with broad-panel next-generation sequencing, so that we don’t miss some of these rare but important targets. Finding one of these has a huge impact for patients to be able to go on a pill and avoid systemic or intravenous treatments for later on in their treatment course.

Q: We know the positive that came out of 2020 for patients with lung cancer, but were there any disappointments?

CARLISLE: Maybe I’m a glass-half-full person, but I think there are far more positive [than negative] things to talk about. For instance, there are 4 new FDA approvals for immunotherapy agents that we already had but can now use in new settings. To start, atezolizumab (Tecentriq) now has an indication in PD-L1–high patients. We can now use ipilimumab (Yervoy) and nivolumab (Opdivo) either as a chemotherapy-sparing agent, [due to results] from CheckMate 227, or we can use nivolumab plus 2 cycles of chemotherapy, [due to results] from CheckMate 9LA. This gives us more options, which is only better for patients.

In addition, the advancements in lung cancer don’t apply just to NSCLC; advances were made in small cell lung cancer (SCLC) as well. Chemotherapy plus durvalumab (Imfinzi) for extensive-stage SCLC was studied in the CASPIAN trial and is now an approved regimen. We also have lurbinectin (Zepzelca), which was granted FDA accelerated approval back in June, for patients whose SCLC cancer progressed after platinum-based chemotherapy. While this is a standard cytotoxic agent, it utilizes a new mechanism of action: It inhibits transcription by binding to certain regions of the DNA, stopping the polymerase and leading to DNA breaks that result in cell death. It showed a good response rate of 35% in 105 patients treated, with a median duration of response of 5 months. These new options for SCLC and these new immunotherapy targets [add up to] really just more good news from 2020 in lung cancer.

Q: When it comes to utilizing these existing immunotherapies in new or different settings, how do we find the patient populations or proper combinations to elicit these positive results?

CARLISLE: [The answer is] due diligence: needing to try each of these agents in the specific cohort that they’ll be used in. While we think of checkpoint inhibitors—agents targeting PD-1 or PD-L1—as all very similar and working on the same pathway, there are nuanced differences [among them]. We really need to do the studies and not assume results. It just takes time to get those done.

Another really promising [development] this year has been more long-term follow-up data. We now have 5-year survival rates from patients with high PD-L1 expression on pembrolizumab (Keytruda) monotherapy, PD-L1–high disease is seen in 30% of patients with NSCLC, and the 5-year survival rate from some of the initial trials is up to 32%. This is [very] important. When I meet a patient with newly diagnosed stage IV NSCLC, I [can] say this isn’t curable, but it’s treatable, and in some cases, it can become like a chronic disease.

A big question that remains moving forward is understanding how long we need to treat these patients. Some reports show that stopping [treatment] at 1 year causes more recurrences than does continued treatment with a PD-1 inhibitor. But I think we need more data to determine how long to treat people, and additional biomarkers to know who is more likely to have a long-term response.

We also have additional data for patients with stage III NSCLC. We have 4-year follow-up data on 1 year of durvalumab, following chemotherapy and radiation, and the survival rate from those data is now 47%; about double what it was before the addition of immunotherapy. All of this information is really helpful for patients and families to have, to give them kind of concrete numbers showing that some people are living longer.

Q: What are you hoping for in 2021 in terms...
of further lung cancer treatment advances?

CARLISLE: From a research perspective, I’m hoping for approvals for a couple of additional new targets. One of the most exciting areas is targeting KRAS, specifically KRAS G12C. We’ve known about KRAS mutations in lung adenocarcinoma for decades, and we know that various KRAS mutations affect about 30% of patients with lung adenocarcinoma, but we haven’t been able to target them. Recently, though, it was noted that specifically the G12C mutation creates a binding pocket, and now a couple of inhibitors specifically target KRAS G12C. One, AMG 510, which was recently reported, showed confirmed response rates of 32% and a disease control rate of nearly 90% in patients with lung cancer. However, 3% to 4% of patients with lung cancer can have HER2 kinase domain mutations or insertions. While a lot of the tyrosine kinase inhibitors that also can inhibit HER2 haven’t been effective, we’ve seen some very exciting data about antibody-drug conjugates—specifically, a study about trastuzumab deruxtecan (Enhertu), which works by using an antibody to bring a cytotoxic agent or payload to cells that express HER2. In this study, the response rate was more than 60%. So, I’m hoping that in 2021 we can see [these] 3% to 4% of patients with HER2-mutated NSCLC have an FDA-approved treatment option, and another 13% of patients with KRAS G12C mutations have a targeted therapy option.

Another wish I have for 2021 is that we use data that we already know about: the lung cancer screening data, which are unfortunately underutilized. We have the long-awaited results from the NELSON study, a screening trial that looked at low-dose CT scans and lung cancer mortality. Specifically, it looked at scans at baselines of 1, 3, and 5 years in patients who were aged 50 to 70 years and were current or former smokers. This showed that proper screening leads to a clear decrease in lung cancer–specific mortality. So, there are broadened screening guidelines, and really, we know that the earlier lung cancer is diagnosed, the easier it is to treat.

In 2021 I hope we’ll also see more data about using immunotherapy in earlier lines of lung cancer treatment, and about incorporating targeted therapy options earlier in the disease course. This year, we saw some impressive data from the ADAURA trial looking at EGFR adjuvant treatment with osimertinib (Tagrisso), with a remarkably low hazard ratio for disease recurrence. While we’re still awaiting long-term overall survival data, we’ve learned so much in patients with advanced disease that may benefit patients with earlier-stage disease, so I hope to see some of those data come out next year as well.

Finally, going back to 2020, we did get data from the American Cancer Society reported back last January, which showed the largest single-year decrease in cancer mortality, a drop largely attributed to reduction in lung cancer deaths: I think it went down 2.2% from 2016 to 2017. Some of this is related to fewer people smoking, but it’s also certainly related to all these targeted therapy options and longer-term survival with immunotherapy, so what we’re doing is actually making an impact.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
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)*

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)*.
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.

* 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.

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

——— Studied in the phase 3 ICARIA-MM trial, which included ——— patients with poor prognostic factors

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.

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.

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.
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**

**Probability of PFS (%)**

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Pd</th>
<th>SARCLISA + Pd</th>
</tr>
</thead>
<tbody>
<tr>
<td>153</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>106</td>
<td></td>
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<td>63</td>
<td>89</td>
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<td>51</td>
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<td>33</td>
<td>52</td>
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<tr>
<td>17</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The median time to first response among responders with SARCLISA + Pd was 35 days vs 58 days with Pd.

**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 10 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.

with a 0.22 micron in-line filter (polysulfone (PES), polysulfone, or nylon).
• The infusion solution should be administered for a period of time that may be extended if the infusion rate is decreased (see Table 2).
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 solution concomitantly in the same intravenous line with other agents.

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

Brief Summary of Prescribing Information

1 PATIENT USAGE
SARCLISA 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.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
• Administer pre-medication medicines [see Dosage and Administration (2.2)].
• SARCLISA should be administered by a healthcare professional who has demonstrated access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur [see Warnings and Precautions (5.7)].

The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone according to the schedule in Table 1 [see Clinical Studies (14) in the full prescribing information].

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone

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

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. SARCLISA is used in combination with pomalidomide and dexamethasone.

Missed SARCLISA Dose
If planning to miss a dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.2 Recommended Premedications
Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions [see Dosage and Administration (2.2)].
• Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age).
• Acrilevame 650 mg to 1000 mg orally (or equivalent).
• H2 antagonists.
• Diphosphonate 25 mg to 50 mg orally or intravenously (or equivalent) if the intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backbone treatment, before SARCLISA and pomalidomide administration. Administer the recommended premedications 15 to 60 minutes prior to starting a SARCLISA infusion.

2.3 Modifications
No dose reduction of SARCLISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematologic toxicity [see Dosage and Administration (2.5)].

For information concerning drugs given in combination with SARCLISA, see manufacturer’s prescribing information. For information concerning drugs that are administered concomitantly 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 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 discoloration prior to administration, whenever solution and container permit.
• Remove any 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 dilution bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polivinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyly 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, polybutadiene (PBD), or polivinylurethane (FPU) with a 0.22 micron in-line filter (polysulfone (PES), polysulfone, or nylon).
• The infusion solution should be administered for a period of time that may be extended if the infusion rate is decreased (see Table 2).
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 solution concomitantly in the same intravenous line with other agents.

Infusion Rates
• Following administration, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental changes in the infusion rate should be considered only in the absence of infusion-related reactions [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Initial Rate</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL</td>
<td>25 mL/hour</td>
<td>For 60 minutes</td>
</tr>
<tr>
<td>Second infusion</td>
<td>50 mL/hour</td>
<td>Increase by 10 mL/min for each of the next 10 minutes to 200 mL/hour</td>
<td></td>
</tr>
<tr>
<td>Subsequent infusions</td>
<td>250 mL</td>
<td>200 mL/hour</td>
<td>For 30 minutes</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 WARNINGS AND PRECAUTIONS
5.1 Infusion-Related Reactions
Infusion-related reactions have been observed in 39% 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 the cases. The infusion-related reactions of an infusion-related reaction included dyspnea, cough, chills, and nausea.

The most common severe signs and symptoms included hypotension and dyspnea [see Adverse Reactions (6.1)]. To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with dexamethasone, H2 antagonists, diphosphonate, or equivalent; dexamethasone [see Dosage and Administration (2.2)]. 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 persist, administer pre-infusion medications and of the backbone treatment, before SARCLISA and pomalidomide administration. Administer the recommended premedications 15 to 60 minutes prior to starting a SARCLISA infusion.

5.2 Neutropenia
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 [see Drug Interactions (7.1)].

5.3 Second Primary Malignancies
The safety of SARCLISA was evaluated in ICON-MM, a randomized, open-label clinical trial in which patients who had previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, <75 years of age, ≥75,000 cells/millim, absolute neutrophil count ≥1 × 10⁹/L, creatinine clearance ≥30 mL/min (MDRD formula), and AST and/or ALT ≤2×ULN. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low dose dexamethasone ( Isa-Pd) (n=152) or pomalidomide and low dose dexamethasone ( Po-Pd) (n=149) [see Clinical Studies (14) in the full prescribing information]. Among patients receiving Isa-Pd, among patients treated with Isa-Pd, compared to 54% of patients treated with Po-Pd, 58% of patients treated with Isa-Pd, and 24% were exposed for greater than 12 months or longer. The median age of patients who received Isa-Pd was 68 years (range 36–83); 58% male, 76% white, and 14% Asian.

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)].

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 Clinical Studies
Multiple Myeloma
The safety of SARCLISA was evaluated in ICON-MM, a randomized, open-label clinical trial in which patients who had previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, <75 years of age, ≥75,000 cells/millim, absolute neutrophil count ≥1 × 10⁹/L, creatinine clearance ≥30 mL/min (MDRD formula), and AST and/or ALT ≤2×ULN. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low dose dexamethasone ( Isa-Pd) (n=149) [see Clinical Studies (14) in the full prescribing information]. Among patients receiving Isa-Pd, among patients treated with Isa-Pd, compared to 54% of patients treated with Po-Pd, 58% of patients treated with Isa-Pd, and 24% were exposed for greater than 12 months or longer. The median age of patients who received Isa-Pd was 68 years (range 36–83); 58% male, 76% white, and 14% Asian.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in ≥5% of patients who received Isa-Pd included pneumonia (22%), upper respiratory tract infections (5%), and febrile neutropenia (5%). Fatal adverse reactions occurred in 11% of patients who received Isa-Pd. Fatal adverse reactions that occurred in more than 1% were pneumonia and other infections (3%).

Permanent discontinuation due to a serious adverse reaction occurred in 2% of patients who received Isa-Pd.

The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).

For information regarding additional clinical trials, please see the full prescribing information.
The most common adverse reactions (≥20%) were neutropenia, 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 Daratumumab 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 + Daratumumab ( Isa-Pd) <em>(N=152)</em></th>
<th>SARCLISA + Daratumumab + Placebo (Pd) <em>(N=149)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>38 1.3 (%)</td>
<td>3 0.0%</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>31 22.3%</td>
<td>23 16.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57 9.0%</td>
<td>42 3.4%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 11.3%</td>
<td>2 1.3%</td>
</tr>
<tr>
<td>Cytopenia and anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17 5.0%</td>
<td>0 12.1%</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>26 2 –</td>
<td>19 0.7 –</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 0 9 0 –</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 1.3 –</td>
<td>3 4.0 –</td>
</tr>
</tbody>
</table>

CTCAE version 4.03

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

1 Upper respiratory tract infection includes bronchiolitis, bronchiitis, bronchitis viral, chronic sinusitis, fungal pnemonitis, parainfluenza virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

2 Dypsnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4: Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment – ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter (in %)</th>
<th>SARCLISA + Pomalidomide + Daratumumab ( Isa-Pd) <em>(N=152)</em></th>
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<tr>
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<td>Thrombocytopenia</td>
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Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment – ICARIA-MM

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Conclusion

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), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

8.2 Lactation

Reduction of IgG levels in breast milk is not expected; therefore, breast feeding is not expected to affect the drug effectiveness.

8.3 Females and Males of Reproductive Potential

8.3.1 Pregnancy

8.3.2 Pediatric Use

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, 55% (396 patients) were 65 and over, while 14% (92 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 and over and younger 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, monitor the patients for signs and symptoms of adverse effects and take all appropriate measures immediately.

Manufactured by: sarofin-events U.S. LLC Bridgewater, NJ 08807 A SANOFI COMPANY U.S. License No. 1752 SARCLISA is a registered trademark of Sanofi ©2020 sarofin-events U.S. LLC ISA-BPLR-SA-MAR20 Revised: March 2020

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Patient-Reported Outcomes of Pain and Related Symptoms in Integrative Oncology Practice and Clinical Research: Evidence and Recommendations

W. Iris Zhi, MD, PhD; Danielle Gentile, PhD; Maggie Diller, MD; Anita Kinney PhD, RN; Ting Bao, MD, DABMA, MS; Viraj Master, MD, PhD, FACS; Xin Shelley Wang, MD, MPH

**ABSTRACT:** Pain is a primary concern among patients with cancer and cancer survivors. Integrative interventions such as acupuncture, massage, and music therapy are effective nonpharmacologic approaches for cancer pain with low cost and minimal adverse events. Patient-reported outcomes (PROs) that have been validated in many clinical and research settings can be used to evaluate pain intensity, associated symptom burden, and quality of life. Clearly defined, reliable PROs can improve patient satisfaction and symptom control. As integrative oncology continues to evolve and expand, cancer-related pain PROs must be standardized to accurately guide clinicians and researchers. Well-validated pain PROs, such as the Brief Pain Inventory, are among the most commonly used for pain intensity assessment. Multiple symptom assessment tools such as the MD Anderson Symptom Inventory, the Memorial Symptom Assessment Scale, the Edmonton Symptom Assessment System, and the Patient-Reported Outcomes–Common Terminology Criteria for Adverse Events measurement system can also capture pain-associated symptom burden. Electronic PROs provide flexibility in collecting and analyzing PRO data. Clinical trials using carefully selected PROs and rigorous statistical analysis plans are fundamental to conducting high-quality integrative oncology research and promoting utilization of effective integrative interventions to improve patient outcomes. In this review, we aim to summarize current, validated PROs specific to cancer-related pain to aid integrative oncology clinicians and researchers in patient care and in study design and implementation.

**Introduction**
Currently, there are approximately 17 million cancer survivors in the United States. This number is projected to increase to 22 million by 2030 due to dramatic decreases in mortality secondary to novel anticancer therapies. In addition, the American Cancer Society estimates that approximately 1.8 million people will be newly diagnosed with cancer in 2020. Patients with cancer are at significant risk for chronic physical and psychological symptoms. Despite cancer treatment advancements and multidisciplinary approaches, cancer pain remains a common and challenging issue affecting up to 66% of patients with cancer. Furthermore, cancer pain management is often suboptimal due to patients’ vulnerability, their reluctance to report pain, communication challenges with their care team, and health barriers and disparities.

Oncology clinicians use pharmacologic and nonpharmacologic interventions to manage cancer-related pain. Commonly used conventional treatments include opioids, anticonvulsants, muscle relaxants, and topical or local injections;
however, these are often expensive and associated with adverse events (AEs). Nonpharmacologic integrative oncology interventions include acupuncture, massage therapy, music therapy, yoga, meditation, tai chi, qigong, and nutrition and lifestyle changes, among others. Evidence suggests that these therapies can effectively alleviate cancer pain and associated symptoms while improving quality of life (QOL), with relatively low cost and fewer AEs than pharmacologic agents (with the exception of some over-the-counter medications such as acetaminophen or ibuprofen, which can have serious AEs).11-13

Consequently, many professional societies, regulatory bodies, and governments now recommend that comprehensive, evidence-based, patient-centered pain management approaches include nonpharmacologic treatment options. The 2016 CDC guidelines recommend nonopioid therapy as the preferred management strategy for chronic pain.14 Both the American Society of Clinical Oncology (ASCO) clinical practice guideline and the National Comprehensive Cancer Network guideline recommend nonpharmacologic interventions, including acupuncture and massage, to treat cancer pain alongside conventional care.15,16 Since 2018, the Joint Commission has also required nonpharmacologic modalities for pain management.17

Accurately assessing patients’ symptoms, the impact of symptoms on QOL, and response to treatment are critical factors for improving patient outcomes, care quality assessment, and clinical research. To guide industry in including patient-reported outcomes (PROs) in medical product development, the Food and Drug Administration (FDA) defined PROs in 2009 as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.”18 PROs can be collected by written questionnaires, in-person interviews, phone conversations, and digital technology. Well-defined and reliable PROs have been shown to improve patient satisfaction and symptom control in patients with and without cancer.19 Pain PROs can also be used to study patient-physician communication outcomes, patient compliance and satisfaction, and quality improvement and performance measures. In addition, results of PROs provide evidence that may impact regulatory decisions.20 However, while PROs are useful for patient assessment, the lack of coherent practices creates challenges in utilizing and interpreting them effectively.

The Society for Integrative Oncology (SIO) promotes rigorous, evidence-based, comprehensive complementary approaches to cancer care. In this article, we review and summarize evidence for commonly used cancer pain PROs in the setting of acute and chronic cancer pain and discuss implications for their use in routine integrative oncology care and clinical research. Our primary focus is on providing guidance for how to use PROs to evaluate chronic cancer pain, bone metastases–related pain, and acute pain after oncological surgery or interventions. Patients with chemotherapy-induced peripheral neuropathy (CIPN) often experience neuropathic pain in their hands and feet, along with numbness, tingling, and other symptoms such as weakness and dysfunction that disrupt their daily activities. While painful neuropathy is an important symptom, multiple validated neuropathy-specific PROs to characterize neuropathic pain and neuropathy severity already exist.21-23 Thus, PROs to assess CIPN is beyond the scope of this review and will not be discussed in detail.

**Cancer Pain Patient-Reported Outcome Measures**

Cancer pain PRO measures should be reliable, validated, and easy for providers, patients, and investigators to use. They may be qualitative or quantitative, or include both elements. Quantitative measures include pain intensity, severity, and impact, while qualitative pain PROs usually include evaluation of pain quality, history, alleviating or aggravating factors, and pain expectation. See the Table for a summary of the current most commonly used cancer pain PROs.

**Pain Intensity Assessments**

The most commonly used quantitative pain PRO is pain intensity. This assessment is straightforward and cost-effective, while minimizing bias from health care professionals. Patient-reported pain intensity objectively measures pain severity and impact on QOL, as well as indications for intervention. The most commonly used methods for determining patient-reported pain intensity are numerical rating scales (NRS), verbal descriptor scales (VDS), and visual analogue scales (VAS). NRS, VDS, and VAS are highly intercorrelated and reliable.24 NRS are more reliable than VAS in clinical trials, especially among patients with low socioeconomic status.25 Numerical rating scales have been validated in clinical and research settings as standard pain measures. One of commonly used NRS, the Brief Pain Inventory (BPI) uses an 11-point pain intensity scale ranging from 0 (“no pain”) to 10 (“worst pain imaginable”); it is among the most widely used NRS pain scales developed specifically for patients with cancer-related pain.26 It is a validated measure of pain intensity and is sensitive to changes over time.27,28 Patients can rate their pain as “right now,” “average,” “at its least in the past 24 hours,” and “at its worst in the past 24 hours.” Furthermore, the BPI provides information on how pain interferes with daily functioning in 7 aspects: general activity, walking, mood, sleep, work, pleasures in life, and social activity. The BPI is highly reproducible and results are comparable between patient self-administration and interviewer administration. In a study conducted by ECOG, the BPI was used...
to determine the prevalence and severity of cancer pain among 1261 patients with cancer from 80 cancer centers in the United States.29 The investigators demonstrated that the BPI was highly consistent with other pain measures and interference factors associated with pain intensity.26 The BPI has a few additional advantages compared with other pain assessment tools: It is brief (can be completed within 5 minutes), can be self-administered by the patient, can be completed remotely by phone or via telemedicine, and is available in multiple languages.31,32

Verbal descriptor scales (VDS) and verbal rating scales (VRS) ask patients to categorize their pain intensity as “none,” “mild,” “moderate,” or “severe.”33,34 Patients self-define these categories; they can be highly variable due to factors such as age, gender, race/ethnicity, language, and culture.35 Visual analogue scales (VAS) determine pain severity by asking patients to indicate a position along a continuous line between 2 end points, one end representing “no pain” and the opposite end representing “worst pain imaginable.”36,37 However, there are some issues with VAS, such as patients often drawing a line in the middle. While VAS has been proven useful in clinical and research settings, it may be difficult for some patients to comprehend.38,39

**Pain Relief and Patient Satisfaction Scales**

Pain relief and patient satisfaction scales are important tools for evaluating PROs and response to treatment. They can be administered at different time points to provide information regarding the immediate and long-term effects of a pain intervention.

The pain relief scale (PRS) measures changes in pain intensity over a period of time.38 Patients are asked to rate their pain intensity changes on a scale that includes “worse,” “the same,” or “complete relief.” The PRS may be useful for capturing response shifts in longitudinal pain assessment.39 However, the most popular measurement of pain reduction has been the pain score change with repeated assessment of pain severity.

The Patient Satisfaction Scale (PSS) asks patients to rate their satisfaction with their current pain management on a scale of 1 (“very dissatisfied”) to 5 (“very satisfied”).40 This scale reflects patient preferences for and expectation of pain relief and is commonly used in pain management quality reassurance.41 Results may be misleading, as evidence suggests that patients will rate their satisfaction levels as high despite having moderate-to-severe pain.42 As such, results from the PSS should be carefully interpreted with consideration for patient preferences, expectations, their confidence in providers, presence of adequate social support, and history of depression.42

**Other Patient-Reported Outcome Measures for Cancer-Related Pain**

The Pain Interference Scale is part of the BPI and measures the impact of pain on functional status. It has been validated in many diseases and acute or chronic pain conditions, including bone metastases and cancer-related neuropathy, and has been found reliable and sensitive to treatment dose response.43-45

The Patient-Reported Outcome–Common Terminology Criteria for Adverse Events (PRO-CTCAE) measurement system includes cancer pain as an important symptom toxicity measure and was developed based on the Common Terminology Criteria for Adverse Events in cancer clinical trials by the National Cancer Institute. It assesses pain frequency, severity, interference, and attributes. PRO-CTCAE can be implemented electronically and has been validated in more than 30 languages. It has demonstrated acceptable validity and reliability.46-48

Health-related quality-of-life (HRQOL) measures include the Short-Form 36 questionnaire, the European Organization for Research and Treatment for Cancer Quality-of-Life questionnaire, the Functional Assessment of Cancer Therapy, and the Patient-Reported Outcomes Measure Information System. These forms often include pain as a subscale and have been incorporated in many pain trials to assess the effects of an intervention on HRQOL.49,50 HRQOL evaluates 4 dimensions: physical function, psychological function, social function, and symptoms related to disease or treatment. In cancer patients, pain severity is negatively associated with HRQOL. Among those with moderate-to-severe pain, HRQOL was significantly decreased compared with patients without pain or with only mild pain.51 Both ASCO and the FDA recommend HRQOL as an important end point in cancer patients secondary to survival.52,53

Symptom burden measures evaluate the symptoms associated with cancer pain such as fatigue, anxiety, insomnia, and anorexia. These measures are designed to capture multiple symptoms and often include assessment of pain and pain treatments (eg, opioids) associated with multiple symptoms. These features can be used to guide pain management. The most commonly used validated, reliable scales are the Symptoms Distress Scale (SDS), the Memorial Symptom Assessment Scale (MSAS), the MD Anderson Symptom Inventory (MDASI), and the Edmonton Symptom Assessment System (ESAS).54-56 It is important to note that increasing pain severity is often associated with increasing symptom burden, but that the relationship is not necessarily linear. Symptom burden measures can be incorporated to determine pain severity and a treatment plan.

**Electronic PROs (ePROs) Assessment**

Electronic medical record (EMR) systems and the widespread use of electronic de-
vices such as computers and smartphones have promoted interest in electronic PROs assessment (ePROs). With ePROs, patients can report their pain symptoms and HRQOL-related dysfunctions via a digital web-based interface, such as a smartphone application (app), a website, or an automated phone system that allows for flexibility in collecting and analyzing PROs data. ePROs data can be directly stored and integrated into the EMR so that the health care team can evaluate a patient’s responses in real time as well as conduct a longitudinal review. It can also generate e-notifications/alerts based on predefined criteria to notify a patient’s health care team immediately and prompt necessary actions.

Results from randomized controlled trials demonstrate improvements in QOL and overall survival by incorporating ePROs into oncology care. For example, using MDASI via an automated phone system significantly reduced pain after thoracic surgery and other symptoms in lung cancer patients. In a randomized controlled clinical trial, Denis et al.

<table>
<thead>
<tr>
<th>TABLE. Summary of Validated Quantitative and Qualitative Patient-Reported Pain Assessment Instruments</th>
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<tbody>
<tr>
<td>Instrument name</td>
</tr>
<tr>
<td>Brief Pain Inventory Short Form&lt;sup&gt;26,44&lt;/sup&gt;</td>
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<tr>
<td>Edmonton Symptom Assessment System Revised&lt;sup&gt;55,56&lt;/sup&gt;</td>
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<tr>
<td>Functional Pain Scale&lt;sup&gt;58&lt;/sup&gt;</td>
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<tr>
<td>Short Form McGill Pain Questionnaire&lt;sup&gt;69&lt;/sup&gt;</td>
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<tr>
<td>Verbal descriptor scales&lt;sup&gt;53&lt;/sup&gt;</td>
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<td>Visual analogue scale&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td>Verbal rating scale&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wong-Baker FACES® Pain Rating Scale&lt;sup&gt;70&lt;/sup&gt;</td>
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</table>
showed improvement in overall survival in early-stage lung cancer patients using web-based ePROs.59 During the recent coronavirus disease 2019 (COVID-19) pandemic, telemedicine has been adapted quickly to continue clinical care while minimizing the risk of COVID-19 exposure.59,60 ePROs could have a unique advantage in this setting if health care providers utilize them for remote monitoring of symptoms to facilitate communication between patients and their care teams. They may also be used as early interventions to reduce emergency department visits and hospital stays.

Application of Pain PROs in Integrative Oncology Clinical Research
Integrative approaches to pain relief such as acupuncture, massage, yoga, qigong, tai chi, and meditation require frequent symptom assessment. Standardized, cancer-specific pain PROs can be used to assess pain severity, intensity, pain interferences, satisfaction, and HRQOL during the treatment course. Collection of PROs at multiple time points, including before and after treatment, allow for the capture of longitudinal information to guide appropriate intervention. Assessments should be validated, sensitive, and easy to administer and interpret. To define pain severity, health care providers and investigators should use validated and reliable measures that categorize pain, such as the BPI. To measure pain relief effects, they can incorporate pain relief scales or patient satisfaction scales. Other outcomes such as pain interference, HRQOL, MDASI, ESAS, or MSAS enhance comprehensive pain assessment in addition to pain intensity, and they include symptoms associated with pain, QOL, and patient satisfaction with pain relief. While multiple PROs can be utilized simultaneously, a mixed model of evaluation may lead to heterogeneous results that are difficult to interpret. Respondent burden is also a consideration. Thus, providers and investigators must identify the specific clinical issue of interest and select the most appropriate PROs that align with the intervention.

Multiple working groups have made enormous efforts to address the methodological issues in study design and interpretation of results associated with utilizing PROs in clinical trials.41-64 When designing a clinical trial to evaluate the effectiveness of integrative interventions to treat cancer pain, substantial differences in reporting outcomes from using a combination of scales can cause confusion in the interpretation and generalizability of research findings.

Careful selection of the most appropriate PROs is essential for the conduct of a successful clinical trial. It is important to consider the following key elements: First, identify the specific population for the intervention of interest. For example, certain pain characteristics, such as bone pain related to metastases or acute postprocedure pain, may respond to acupuncture or massage differently. Thus, clearly defining the target population—for example, cancer survivors with chronic pain or patients with active painful bone metastases—can increase homogeneity and limit confounding factors. Second, select the most appropriate primary or secondary end points such as pain intensity, HRQOL, analgesic reduction, or symptom burden associated with pain. The selected end points should be based on a carefully developed hypothesis and potential outcomes of interest (eg, the MDASI burden questionnaire for a study of music therapy for reduction of cancer pain-associated symptoms, or an NRS scale to measure pain intensity for a study of acupuncture for acute bone metastases pain). Third, create a rigorous study design and statistical analysis plan to calculate study sample size and expected PROs changes. Using the example above, an NRS reduction of 2 points or >20% has been correlated with minimal pain improvement in patients regardless of baseline pain severity.45 Pain score reductions of less than 2 points may be statistically significant but might not be clinically meaningful, such as when the pain score remains mild (eg, 0-4/0-10) or severe (eg, 7-10/0-10). Therefore, it is important to observe the reduction in pain from moderate/severe to none/mild through an effective intervention. Fourth, the study should have a detailed plan for collecting PROs that is concise and easy for patients; it should include defined data collection time points, determination of whether data will be collected in-person or electronically (eg, phone, apps, or online surveys), and a data safety plan. Lastly, it is necessary to thoroughly plan for all possible pitfall scenarios, such as incomplete or missing data.

How to Interpret PROs
Comparative Effectiveness Research in Integrative Oncology
Methodologies are unique to evaluate integrative oncology intervention clinical trials that often focus on symptom management and improving QOL. Survival benefit is less likely to be the primary goal. Thus, clinical trials evaluating integrative therapies must include patients’ perceptions of treatment expectancies, intervention effectiveness, AEs, and overall QOL. PROs are a valuable tool in comprehensive pain assessments, which can be inconsistent when based on grading assessments from providers and care teams.46 The ASCO Quality Care Committee and the National Quality Forum recently recognized the need for clearly defined PROs specific to cancer pain, particularly pain from bone metastases, and have prioritized establishing recommendations regarding their use.46 Current guidelines and recommendations for the use of PROs in clinical research need to be adapted to meet the specific needs of integrative oncology research and practice. Efforts to increase awareness of robust clinical evidence surrounding the effectiveness of integrative interventions for cancer-related pain and enhance widespread utilization of these.
techniques are needed.\textsuperscript{44} PROs are subjective; however, the evaluation of PROs must be scientifically sound. Readers must have full knowledge of existing evidence and gaps based on extant literature in the identified study population to properly interpret and understand clinical trial results and examine the study hypothesis. Further, since PROs are often multidimensional, it is important to clearly identify the PRO as the primary or secondary end point linked to the study hypothesis in order to determine its rationale and significance. The method of analysis in PRO research was adapted from therapeutic intervention trials, but because PROs are multidimensional and collected at multiple time points, statistical analyses are at risk of false positive results. Readers must be aware of this bias, particularly when the study reports positive results for multiple end points without providing detailed documentation of the statistical analysis plan. The study should also have a clearly defined statistical plan to handle missing data. Readers must exercise caution regarding the sensitivity and validity of PROs before accepting the results and applying them to daily practice and clinical research. Standardizing cancer-specific PROs will aid in study design and statistical planning in integrative oncology clinical trials so that researchers and providers can utilize novel findings in large-scale meta-analyses and quickly adapt them for clinical practice.

**Barriers and Limitations of Pros in Integrative Oncology Research**

Because pain is subjective in nature, using PROs to assess pain and pain-related symptoms provides important patient-centered feedback and serves as a platform for effective communication between patients and clinicians. Concurrently, PROs can be challenging because of their subjectivity. Patients may not be aware of the importance of PROs, which can lead to noncompliance with pain treatment regimens. The utility of PROs in the patient-centered care model may also lack linguistic validation and cultural adaption, causing reporting bias. However, based on international studies, well-validated tools in different languages have minimal negative impact on pain and other PROs.\textsuperscript{37} Patient and advocate concerns about PROs should be effectively communicated with the clinical team and appropriate education materials and trainings should be provided for patients and their care partners.

With multiple validated PRO tools available, choosing the most suitable PRO can be overwhelming. For this reason, we have included a summary of validated cancer-related pain PRO instruments in the Table. Integrative oncology researchers and practitioners may use it to select appropriate pain-related PROs for their specific interests and needs.

Another major challenge is the implementation of PROs into clinical practice and research. Implementation involves training of physicians, nurses, and research staff, as well as providing clear instructions to patients; systemic—and ideally automatic—collection of PROs into EMRs; and adequate data storage. All of these factors can be labor-intensive and involve a sharp learning curve for those who are new to collecting PROs. Practitioners and researchers should also be mindful of the potential reporting burden for patients who may be expected to answer other symptom assessments in addition to those about pain. Guidance from government and support from institutional leadership can facilitate this process. Furthermore, the methodology used to analyze PROs is imperfect. Multidimensional and multiple time-point PROs collection can lead to statistical drawbacks and pitfalls.\textsuperscript{46} Rigorous methodology development to overcome current challenges remains the priority in PRO research.

**Conclusions and Recommendations**

The SIO Research Committee strives to increase awareness of current national and societal guidelines and recommendations related to PROs to promote their adoption into clinical practice and research. Multiple validated and reliable PROs accurately assess pain and related symptoms in cancer patients and survivors. In integrative oncology practice, these PROs have essential value and should be incorporated routinely in clinical care.

Based on available evidence, we recommend the following commonly used PROs to assess cancer pain and related symptoms, alphabetically: BPI, ESAS, MDASI, MSAS, and PRO-CTCAE. These tools are essential to the integrative oncology care team and should be incorporated routinely into clinical practice. Electronic PROs provide flexibility in collecting and analyzing PRO data. Education regarding pain PRO tools should be extended to patients, caregivers, the entire cancer care team including physicians and nurses, the research team, and institutional leadership. Infrastructure to streamline PRO collection, data storage, and safety are also necessary for using PROs in daily practice.

The PROs described in this paper are vital for integrative therapy development, with the primary goal of reducing symptom burden and improving QOL in people affected by cancer. When studying the effectiveness of integrative inventions in cancer pain, PROs may be the primary or secondary end points with a specific hypothesis, clearly defined population, and detailed statistical plan. The FDA has put forth standard methods of applying PROs in clinical trials; researchers should apply these standards to pain intervention trials utilizing integrative techniques.\textsuperscript{18} Detailed strategies for PRO collection, data analysis, and handling missing data are key steps to success. Lastly, the timely publication of high-quality research findings will facilitate dissemination of information to ensure that clinical practice can be
adjusted accordingly, and patient outcomes can be maximized.

With the increasing incidence and prevalence of cancer in the United States, accurate and frequent assessment of pain and pain-related symptoms is paramount. Validated PROs specific to cancer-related pain are essential tools in the armamentarium for clinical oncologists and researchers. It is imperative that clinicians understand the role of PROs, as well as their limitations, in both practice and research, so they can be used and interpreted effectively. As the number of integrative interventions for pain and related symptoms continue to increase, PROs will provide insight regarding the effectiveness of these interventions on both the individual and population levels. Use of PROs will lead to the expansion of current evidence-based practice guidelines for integrative oncology practitioners.

**FINANCIAL DISCLOSURE:** The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

**KEY REFERENCES**

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Building on Telehealth’s Momentum

Michael Abrams, MA

The coronavirus disease 2019 (COVID-19) pandemic accelerated the development and deployment of telehealth technology so forcefully that what might have taken years happened, instead, in weeks. Federal regulations that had kept costs of the technology high were waived, while other rules were overturned to give reimbursement parity with that of in-office visits, thus addressing 2 key obstacles that had earlier constrained the wide adoption of telehealth.

Telehealth technology and our digital infrastructure had matured to the point that it could, fortunately, support far broader use just when it was needed. Numerous technology products were available, reasonably user-friendly, and generally affordable—and that was a good thing, because across the nation, it was telehealth or nothing.

Now we are at a critical juncture. The regulatory waivers and increased reimbursement levels were only temporary, which means that as a nation, we must decide whether we will continue to marginalize telehealth technology or allow providers to find ways to integrate it solidly into our care delivery infrastructure.

As is usually the case in health care, a small segment of forward-thinking organizations were using telehealth before the pandemic. But the overwhelming majority of provider organizations had little or no experience with telehealth prior to the pandemic. Because these organizations rely so heavily on fee-for-service reimbursement, the complex regulation of telehealth left them with little curiosity about the technology until COVID-19 struck.

This latter group is the target for what comes next from a regulation and reimbursement point of view. Since most of this latter group is waiting to find out what the regulation and reimbursement will look like, the answers will determine what they do next.

Telehealth was a specific agenda item at the September 3-4 meeting of the Medicare Payment Advisory Commission, where these exact recommendations were discussed. There, handwringing about potential fraud by telehealth companies, plus preliminary data on quality of care that offered mixed support for telehealth, became the rationale for a recommendation to limit some of the telehealth expansions to only those clinicians participating in Advanced Payment Models (APMs) rather than to all fee-for-service clinicians. This recommendation would not allow physicians who do not participate in APMs to be reimbursed for providing telehealth services to patients outside of rural areas, or for providing telehealth services to patients at home. Another of the commission’s recommendations was to return telehealth reimbursement to prepandemic levels.

This kind of thinking reflects a lack of understanding regarding the drivers of change in health care. Micromanaging the use of an innovation and reducing reimbursement to its stifling pre-pandemic level is not a recipe for stimulating the intelligent uptake of telehealth. The truth is that delivery organizations that take accountability for cost and quality seriously are already using telehealth. It’s an important part of the answer to their problem: how to deliver care that is as good or better than the current standard at a lower cost. As we start to see the light at the end of the pandemic tunnel, health care organizations have a lot of momentum with regard to telehealth. The technology infrastructure has been put in place. And research results indicate that many physicians who previously hadn’t paid much attention to telehealth have now discovered that it has value, and likewise, many patients have discovered that telehealth makes more sense in some situations.

We’re at the point where more investment is needed to evaluate how, when, and where to best use the available technology for telehealth. Most provider organizations are waiting for payers to come out with answers to reimbursement and regulatory questions before they expend more resources in this area. It’s pragmatic decision-making: If investment may not prove to be worth providers’ time, effort, and money, then they’ll be loath to opt for it.

While it’s true that innovation sometimes creates opportunities for those who would game the system, it also creates opportunities to improve it. Those who can’t recognize telehealth’s potential won’t use it. Those who can will be grateful for it, and health care consumers grateful in return.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
CONTINUING MEDICAL EDUCATION (CME)

Targeting TIGIT: Strengthening the Immune Checkpoint Blockade

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

• Describe the cellular distribution and physiologic function of T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT)
• Explain the rationale for TIGIT blockade as a mechanism for treating solid tumors
• Assess key data from ongoing clinical trials evaluating emerging TIGIT blocking agents for the treatment of solid tumors

RELEASE DATE: January 1, 2021
EXPIRATION DATE: January 1, 2022

INSTRUCTIONS FOR PARTICIPATION / HOW TO RECEIVE CREDIT

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The introduction of immune checkpoint inhibitors into the therapeutic armamentarium against malignancies successfully catalyzed a paradigm shift into how clinicians approach the management of patients with cancer. Checkpoint inhibitors have become ubiquitous in the consideration of treatment options for patients with numerous cancer subtypes, following the site-agnostic FDA approval for some of these agents. As the importance of immune checkpoint interactions between tumor cells and immune cells has become better understood in recent years, research efforts into identifying novel agents has brought about the emergence of a promising class of immune checkpoint inhibitors that targets a protein heavily involved in tumor cell-regulated immune cell suppression: T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT). The TIGIT pathway includes 3 known primary components: the inhibitory TIGIT receptor expressed on effector lymphoid cells; a competing costimulatory receptor CD226 (DNAM-1), expressed on effector lymphoid cells; and its ligand, CD155 (PVR), expressed on tumor cells and antigen-presenting cells in the tumor microenvironment. Although DNAM-1 binding to PVR activates the immune response, PVR preferentially binds to TIGIT, resulting in suppression of the immune response. Further immune suppression occurs following chronic PVR-TIGIT binding due to the resulting downregulation of DNAM-1. Inhibiting TIGIT prevents its interaction with PVR and the consequential suppression of the immune response. As the TIGIT-PVR interaction is blocked, upregulation of DNAM-1 occurs, allowing its binding to PVR and the subsequent DNAM-1-mediated activation of immune cells.

Luis Paz-Ares Rodriguez, MD, reviews the present clinical understanding of TIGIT including the rationale for its immunotherapeutic targeting in treating numerous cancer subtypes and the potential integration of TIGIT blocking agents into the treatment landscape for patients with cancer across lines of care.

Q: What is the role of TIGIT in tumor cells?
PAZ-ARES: Essentially, TIGIT is mainly another mechanism used by tumor cells to evade immune responses, particularly by their interaction with T cells and natural killer (NK) cells, preventing the immune response against the tumor. There are a number of mechanisms, from which TIGIT is able to create this immunosuppressive environment and evade immune response within a tumor.

Q: What is the rationale for developing therapies that target TIGIT?
PAZ-ARES: Indeed, the interactions among TIGIT, CD155, CD226, CD96, and CD112 are complex. These receptors are expressed mostly on T cells and NK cells. Some of these receptors may trigger immune activating or suppressing signals, and actually, they share certain ligands. TIGIT signaling appears to be for the most part immunosuppressive. There are a number of ways that TIGIT inhibits the innate and adaptive immune response. To summarize—first, one way would be by impeding T-cell function by binding CD155 on dendritic cells. Secondly, TIGIT does have some immune cell-intrinsic inhibitory effects. Indeed, anti-TIGIT antibodies inhibit T-cell proliferation and functioning. Third, TIGIT decreases the CD155-mediated activation of CD226. Fourth, the balance between TIGIT and CD226 expression regulates the effect or function of T cells and NK cells. Lastly, TIGIT augments the immunosuppressive function of regulatory T cells (Tregs).

Therefore, the rationale for developing drugs against TIGIT is to inhibit those 5 main inhibitory functions, an approach that has been substantiated by several preclinical studies. Additionally, tumors often overexpress these receptors, and this has been shown in a number of different tumor types, including colon, breast, lung, pancreatic, melanoma, glioma. Also, the expression of PVR is associated with unfavorable prognosis. We know that anti-TIGIT blocking agents have an effect on preclinical outcomes, and early clinical data suggest that these agents may prevent resistance to other immune therapies, for instance, in tumors becoming refractory to PD-1-targeting agents.

Q: What are some of the key emerging agents targeting the TIGIT-PVR axis currently being evaluated in clinical trials?
PAZ-ARES: Most of these agents block TIGIT itself, and there are a number of these compounds. Tiragolumab is a monoclonal antibody targeting TIGIT. Other compounds include BMS-986207, AB-154, ASP-8374, GBB-A1217, and MK-7684. All of them are in clinical trials for different tumor types. The most common tumor types studied are lung cancer and melanoma.
Another investigational agent, COM701, targets CD112R.17

Q: Which tumor types are these TIGIT-blocking agents currently being evaluated for in clinical trials?

PAZ-ARES: Phase 1 trials have typically been evaluating these agents in solid tumors and include cohorts exploring diseases that are normally responsive to other checkpoint inhibitors, such as melanoma, lung cancer, renal cell carcinoma, and others.1 Phase 3 trials are underway in various tumor types, including tiragolumab in small-cell lung cancer, which is not a typical target of immunotherapy.2 Altogether, a broad spectrum of cancer types are being studied.

Q: What are the key efficacy data from clinical trials evaluating TIGIT-blocking agents?

PAZ-ARES: The most robust clinical trial data that we have at the present time, apart from some responses in Phase 1 trials, are Phase 3 studies of tiragolumab as first-line treatment for patients with non-small cell lung cancer (NSCLC) expressing PD-L1.15,18 The reason for that is that the co-expression with PD-L1 is very relevant in determining response. Those tumors that do not express PD-1 may not benefit at all or at the same magnitude. Indeed, in the CITYSCAPE trial, comparing tiragolumab plus atezolizumab (an anti-PD-L1 agent) with atezolizumab plus placebo, there was a clear increase in response rate for patients receiving tiragolumab plus atezolizumab.18 Importantly, increased response rates were observed only in patients with high levels of PD-L1 expression (more than 50% of tumor cells). In those tumors with moderate PD-L1 expression (1% to 49% of tumor cells), there was no improvement in response rate, and the same was observed in terms of PFS: a substantial improvement for patients with high PD-L1 expression but no increase in those with low-to-moderate expression.

Q: What are some of the major adverse events observed with TIGIT-blocking agents thus far?

PAZ-ARES: In my opinion, these agents are well-tolerated. Adverse events that warrant the need for observation include infusion-related reactions, rash, and transaminitis. Of note, adverse reactions were typically grade 1 or 2, and very few patients had grade 3 or 4 adverse events. Additionally, in the tiragolumab trial, in which 67 to 68 patients were randomized to each arm, the number of patients with adverse reactions was similar in both arms.15,18 The number of patients with grade 3 to 5 events was also similar, and the number of patients with serious adverse events was similar. In addition, the number of patients with adverse events leading to treatment withdrawal was also similar. So, it looks like tiragolumab did not add to the toxicity associated with atezolizumab by much in this study.

Q: What is the role of biomarkers in predicting response to TIGIT-blocking agents?

PAZ-ARES: This area is very much unexplored. At the present time, we have some evidence that tumors with low PD-L1 expression are not achieving a good response rate, based on preclinical and clinical data from trials investigating tiragolumab plus atezolizumab.15,18 Indeed, some of the data in NSCLC suggests that failing to select for highly expressing tumors...
results in much lower activity. However, these data need to be confirmed in larger trials. Secondly, biomarkers related to the mechanism of action, such as PVR, should be explored. Tumor mutational burden, as well as others, such as lymphocyte infiltration and the type of lymphocyte, may be helpful. But those are very much unexplored so far.

**Q:** What are the major challenges that emerged in the development of TIGIT-blocking agents so far?

**PAZ-ARES:** The main issue is that the data seem to suggest that given alone, these agents may not be very effective. Secondly, it looks like the use of these agents requires combining with PD-1 or PD-L1 agents in order to achieve a response. The other issue is that the data suggest that once resistance to PD-1/PD-L1 agents develops, it may not be possible to revert to the use of anti-TIGIT agents, requiring use of these agents in earlier lines of treatment.

**Q:** How do you anticipate TIGIT blockers may be incorporated into cancer treatment if they are approved?

**PAZ-ARES:** These agents will more likely be used in combination with other therapies. Perhaps when we better dissect the effects of anti-TIGIT therapy in different tumor types, we may see that in specific tumors or histological profiles that they are effective on their own. This would likely be in just a minority of cases. And, of course, CAR T-cell therapy in combination with anti-TIGIT agents could be another approach worth investigating.

**Q:** Is there anything you would like to add regarding TIGIT-targeting agents that we may not have discussed?

**PAZ-ARES:** Since quite a few agents have emerged at once, it will be challenging to see how we can effectively integrate so many agents. This also assumes that the use of anti-TIGIT agents is a truly worthy strategy. There is always a risk with a number of agents competing for the same ‘piece of pie,’ particularly because the amount of data we have so far is limited, which may actually provoke reactions from drug companies, such as making decisions not so much based on science but on strategy to be the first in a given scenario when conducting Phase 3 trials, even if there is not much data to support it, but it would be interesting to see what happens. So I think we should approach the evaluation of these agents in a way that ensures we establish the scientific data before making big decisions.

**KEY REFERENCES**


“Essentially, TIGIT is mainly another mechanism used by tumor cells to evade immune responses, particularly by their interaction with T cells and NK cells.”

- Luis Paz–Ares Rodriguez, MD
A diagnosis of prostate cancer was life-changing news for over 170,000 people per year.

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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 39% 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 Important Safety Information throughout, and Brief Summary of the full Prescribing Information.

**Achieve Greater Outcomes for Your Patients**

The first phase 3 trial of an anti-CD38 mAb in combination with Pd vs Pd alone

**Median PFS of ~1 year with SARCLISA + Pd**

- **SARCLISA + Pd** (n=154)  
  - 11.53 months mPFS  
  - HR=0.596 (95% CI: 0.44, 0.81)  
  - P=0.0010

- **Pd** (n=153)  
  - 6.47 months mPFS  
  - (95% CI: 4.47, 8.28)

**A significant increase in responses shown with SARCLISA + Pd***

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
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<tr>
<td><strong>60.4% ORR</strong></td>
<td><strong>35.3% ORR</strong></td>
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<td><strong>31.8% ≥VGPR</strong></td>
<td><strong>8.5% ≥VGPR</strong></td>
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<tr>
<td>35 days</td>
<td>Median time to first response among responders</td>
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<td>58 days</td>
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*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

- 7% of patients receiving SARCLISA + Pd permanently discontinued treatment due to adverse reactions

Infusion time decreases to 75 minutes starting after the second infusion in the absence of IRRs

**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 the full Prescribing Information.

**SANOFI GENZYME**

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