

# PRACTICAL, PEER-REVIEWED PERSPECTIVES SINCE 1987 ONCOLOGY<sup>®</sup>

NOVEMBER 2020 | Vol 34 • No 11


**SARCLISA<sup>®</sup>**  
 (isatuximab-irfc)

Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

 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, 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010).**

SARCLISA also demonstrated a **significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)\***

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

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.

## 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.

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

## 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.

# 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<sup>1</sup> —

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

Randomized 1:1

**SARCLISA + Pd<sup>a</sup>**  
(n=154)

**Pd<sup>a</sup>**  
(n=153)

<sup>a</sup>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.

- 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,<sup>†</sup> OS

The phase 3 ICARIA-MM trial included patients with poor prognostic factors<sup>1-3</sup>

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

\*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.

<sup>†</sup>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)

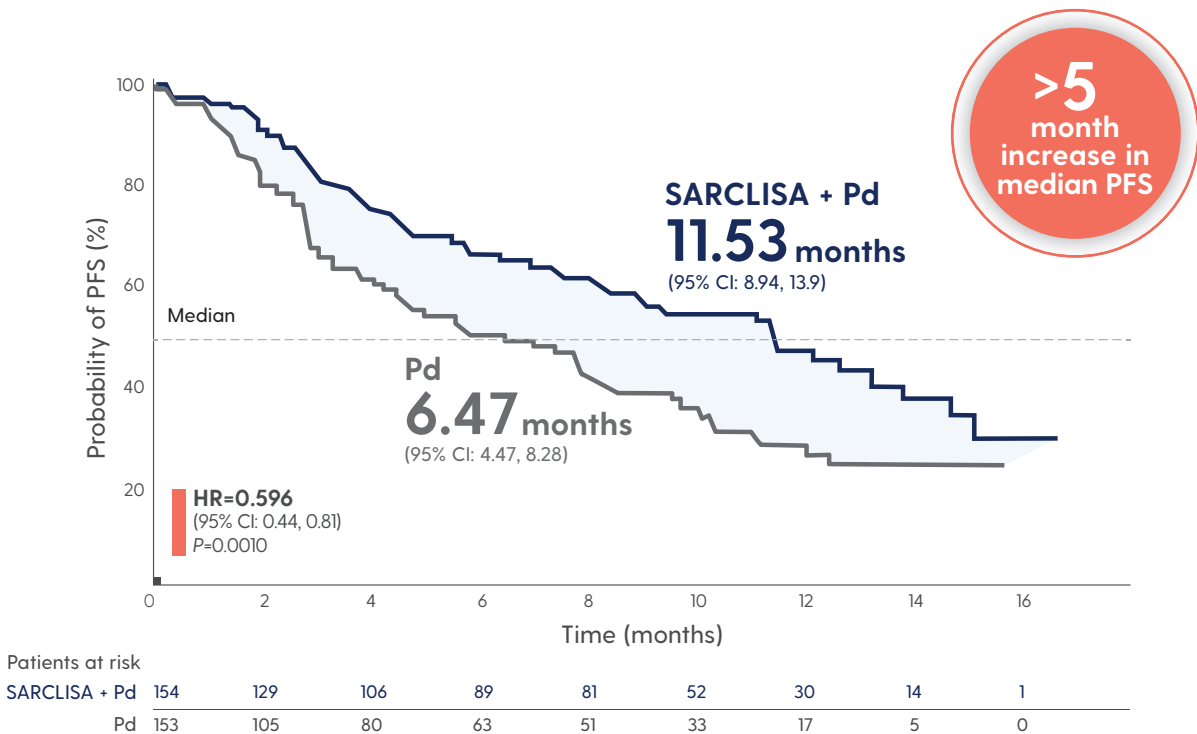
To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H<sub>2</sub> antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support.

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



# SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone<sup>1</sup>



The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.<sup>1</sup>

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.<sup>1</sup>

GREATER  
THAN  
**40%**

**reduction in the risk of progression or death**  
in patients receiving SARCLISA + Pd<sup>1</sup>

## Important Safety Information (cont'd)

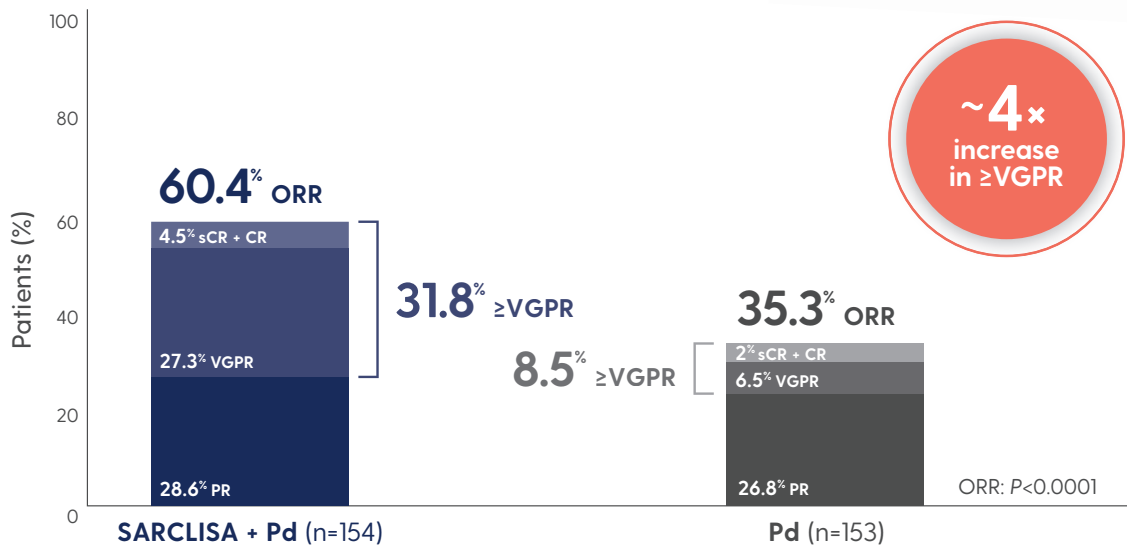
### Infusion-Related Reactions (cont'd)

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<sup>®</sup>**  
(isatuximab-irfc)  
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL

# SARCLISA + Pd Showed a Significant Increase in ORR<sup>1</sup>



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.<sup>1</sup>



**Median time to first response** was 35 days with SARCLISA + Pd vs 58 days with Pd alone among responders<sup>1</sup>

## 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®).<sup>4</sup>

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.

NR=not reached.

## 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%).

**SARCLISA®**  
(isatuximab-irfc)  
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL



**SARCLISA®** (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**

Cycle	Dosing schedule
Cycle 1	Days 1, 8, 15, and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

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 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 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 backbone treatment, before SARCLISA and pomalidomide administration. Administer the recommended premedication agents 15 to 60 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 concerning 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 diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

**2.5 Administration**

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU])

**Rx Only**

- with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (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 infusion solution concomitantly in the same intravenous line with other agents.

**Infusion Rates**

Following dilution, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of 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**

	Dilution Volume	Initial Rate	Absence of Infusion-Related Reaction	Rate Increment	Maximum Rate
First infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/hour every 30 minutes	200 mL/hour
Subsequent infusions	250 mL	200 mL/hour	—	—	200 mL/hour

**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 most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension 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 of the initial infusion 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, as shown in Table 2 [see Dosage and Administration (2.5)]. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate 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). 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%) [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 delay SARCLISA dose until neutrophil count recovery to at least 1.0 × 10<sup>9</sup>/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

**5.3 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, as per International Myeloma Working Group (IMWG) guidelines.

**5.4 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 [see Drug Interactions (7.1)]. **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 [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 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 [see Use in Specific Populations (8.1, 8.3)]. 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.

**6 ADVERSE REACTIONS**

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-Related Reactions [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Second Primary Malignancies [see Warnings and Precautions (5.3)]

**6.1 Clinical Trials Experience**

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

**Multiple Myeloma**

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm<sup>3</sup>, absolute neutrophil count ≥1 × 10<sup>9</sup>/L, creatinine clearance ≥30 mL/min (MDRD formula), and AST and/or ALT ≤3 × 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 (Pd) (n=149) [see Clinical Studies (14) in the full prescribing information]. Among patients receiving Isa-Pd, 66% 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 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 (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%]). Permanent discontinuation due to an adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). In addition, SARCLISA alone was discontinued in 3% of patients due to infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).

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 Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial**

Adverse Reactions	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Infusion-related reaction	38	1.3	1.3	0	0	0
<b>Infections</b>						
Pneumonia*	31	22	3.3	23	16	2.7
Upper respiratory tract infection†	57	9	0	42	3.4	0
<b>Blood and lymphatic system disorders</b>						
Febrile neutropenia	12	11	1.3	2	1.3	0.7
<b>Respiratory, thoracic and mediastinal disorders</b>						
Dyspnea‡	17	5.0	0	12	1.3	0
<b>Gastrointestinal disorders</b>						
Diarrhea	26	2	–	19	0.7	–
Nausea	15	0	–	9	0	–
Vomiting	12	1.3	–	3.4	0	–

CTCAE version 4.03  
\*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jirovecii pneumonia.  
†Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenza virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.  
‡Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the hematology laboratory abnormalities in ICARIA-MM.

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

Laboratory Parameter n (%)	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	151 (93)	48 (32)	0	145 (97)	41 (28)	0
Neutropenia	146 (96)	37 (24)	92 (61)	137 (92)	57 (38)	46 (31)
Lymphopenia	140 (92)	64 (42)	19 (13)	137 (92)	52 (35)	12 (8)
Thrombocytopenia	127 (84)	22 (14)	25 (16)	118 (79)	14 (9)	22 (15)

**Description of Selected Adverse Reactions**  
**Infusion-related reactions**  
In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypertension,

and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 55 minutes. In a separate study (TCD 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.  
**Infections**  
In ICARIA-MM, the incidence of Grade 3 or higher infections was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.  
**6.2 Immunogenicity**  
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other isatuximab-irfc products may be misleading.  
In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ADAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

**7 DRUG INTERACTIONS**  
**7.1 Laboratory Test Interference**  
**Interference with Serological Testing**  
SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see *Warnings and Precautions* (5.4)].  
**Interference with Serum Protein Electrophoresis and Immunofixation Tests**  
SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria [see *Warnings and Precautions* (5.4)].

**8 USE IN SPECIFIC POPULATIONS**  
**8.1 Pregnancy**  
**Risk Summary**  
SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see *Data*). There are no available data on SARCLISA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of SARCLISA and 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. Pomalidomide is only available through a REMS program.  
**Clinical Considerations**  
**Fetal/neonatal reactions**  
Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Defer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

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

**8.2 Lactation**  
**Risk Summary**  
There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.  
**8.3 Females and Males of Reproductive Potential**  
**Pregnancy Testing**  
With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.  
**Contraception**  
**Females**  
SARCLISA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations* (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.  
**Males**  
Refer to the pomalidomide prescribing information.  
**8.4 Pediatric Use**  
Safety and effectiveness in pediatric patients have not been established.  
**8.5 Geriatric Use**  
Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 and over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years 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 or symptoms of adverse effects and take all appropriate measures immediately.

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



# ONCOLOGY®

PRACTICAL, PEER-REVIEWED PERSPECTIVES

NOVEMBER 2020 | Vol 34 • No 11

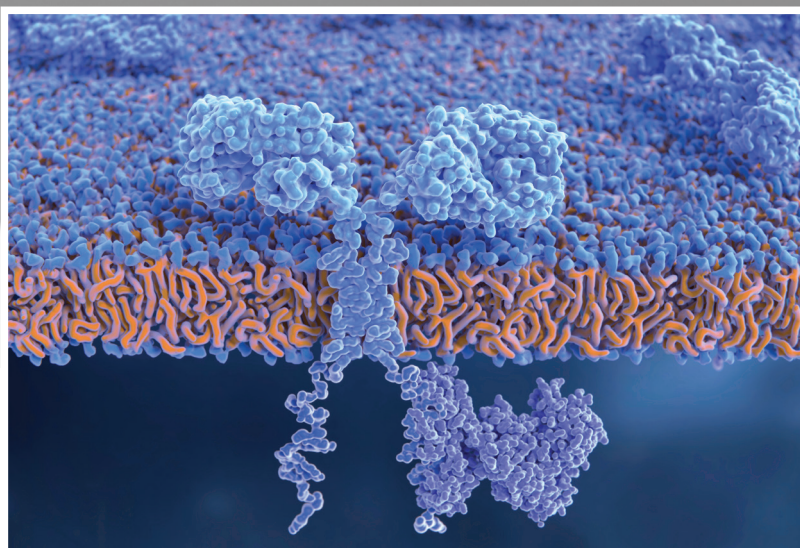


## HEMATOLOGIC MALIGNANCIES

SAGAR LONIAL, MD, ON

# Hitting a New Target in Multiple Myeloma

‘The future, to me, is really exciting.’



**GU Cancer** Incidence of Metastatic Prostate Cancer On the Rise Jason M. Broderick

**Women's Cancer** Pipeline

**Lung Cancer** Progress and Challenges in Non-small Cell Lung Cancer and Colorectal Cancer With Pan-KRAS Inhibitors

Jonathan W. Riess, MD, MS

**GI Cancer** International Society of Gastrointestinal Oncology Abstracts

**Immunotherapy** FDA Approval



FOR THE TREATMENT  
OF METASTATIC  
CASTRATION-RESISTANT  
PROSTATE CANCER (CRPC)<sup>1</sup>

# EXPLORE THE CAPABILITIES

of an innovative abiraterone  
acetate formulation

YONSA® is the only abiraterone acetate that is micronized,  
a process that increases surface area and enables more rapid  
dissolution and absorption.<sup>1</sup>

Discover more at [www.YonsaRx.com](http://www.YonsaRx.com)

## INDICATION

YONSA® (abiraterone acetate) in combination with methylprednisolone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

## Important Administration Instructions

YONSA® may not be interchangeable with other abiraterone acetate products. To avoid substitution errors and overdose, be aware that YONSA® tablets may have different dosing and food effects than other abiraterone acetate products. Patients receiving YONSA® should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

YONSA® can cause fetal harm and potential loss of pregnancy.

Please see the following pages for Important Safety Information and Brief Summary of the Full Prescribing Information.



## IMPORTANT SAFETY INFORMATION, CONTINUED WARNINGS AND PRECAUTIONS

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess: YONSA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA®.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of YONSA® in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials.

**Adrenocortical Insufficiency (AI):** AI was reported in patients receiving abiraterone acetate in combination with corticosteroid, following an interruption of daily steroids and/or with concurrent infection or stress. Monitor patients for symptoms and signs of AI, particularly if patients are withdrawn from corticosteroids, have corticosteroid dose reductions, or experience unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with YONSA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

**Hepatotoxicity:** In postmarketing experience, there have been abiraterone acetate-associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA®, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced YONSA® dose of 125 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt YONSA® treatment and closely monitor liver function.

Re-treatment with YONSA® at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

Permanently discontinue treatment with abiraterone acetate for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of YONSA® re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

## ADVERSE REACTIONS

The most common adverse reactions (>10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

## DRUG INTERACTIONS

Based on *in vitro* data, YONSA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during YONSA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA® dosing frequency only during the co-administration period.

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with an abiraterone acetate single dose equivalent to YONSA® 500 mg. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate.

## USE IN SPECIFIC POPULATIONS

- **Females and Males of Reproductive Potential: Advise male patients with female partners of reproductive potential to use effective contraception.**
- Do not use YONSA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

**Please see following page for the Brief Summary of the Full Prescribing Information.**

**Reference:** 1. YONSA® [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; May 2018.



YONSA is a registered trademark of Sun Pharma Global FZE.  
©2020 Sun Pharmaceutical Industries, Inc. All rights reserved. November 2020 PM-US-YON-0393

**Brief Summary of Prescribing Information for YONSA® (abiraterone acetate) tablets**

This Brief Summary does not include all the information needed to use YONSA safely and effectively.

See full prescribing information for YONSA.

See package insert for full Prescribing Information

Initial U.S. approval: 2011

**INDICATIONS AND USAGE:**

YONSA (abiraterone acetate) is indicated in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer.

**CONTRAINDICATIONS:**

YONSA is contraindicated for use in pregnant women. YONSA can cause fetal harm and potential loss of pregnancy.

**DOSAGE AND ADMINISTRATION:**

Recommended dose: YONSA 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. Patients receiving YONSA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

To avoid medication errors and overdose, be aware that YONSA tablets may have different dosing and food effects than other abiraterone acetate products.

**WARNINGS AND PRECAUTIONS:**

YONSA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with YONSA.

Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity can be severe and fatal. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with YONSA, every two weeks for the first three months of treatment and monthly thereafter.

**ADVERSE REACTIONS:**

The most common adverse reactions ( $\geq 10\%$ ) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities ( $> 20\%$ ) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

**DRUG INTERACTIONS:**

CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during YONSA treatment. If a strong CYP3A4 inducer must be co-administered, increase the YONSA dosing frequency.

CYP2D6 Substrates: Avoid co-administration of YONSA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

**USE IN SPECIFIC POPULATIONS:**

Females: Women who are pregnant or women who may be pregnant should not handle YONSA tablets without protection, e.g., gloves.

Males of Reproductive Potential: Males with female partners of reproductive potential should use effective contraception.

Hepatic Impairment: Do not use YONSA in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Pediatric Use: Safety and effectiveness of abiraterone acetate in pediatric patients have not been established.

**To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555, FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**Manufactured for:**

Sun Pharma Global FZE

**Distributed by:**

Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

YONSA is a registered trademark of Sun Pharma Global FZE

Copyright © 2019 Sun Pharma Global, FZE

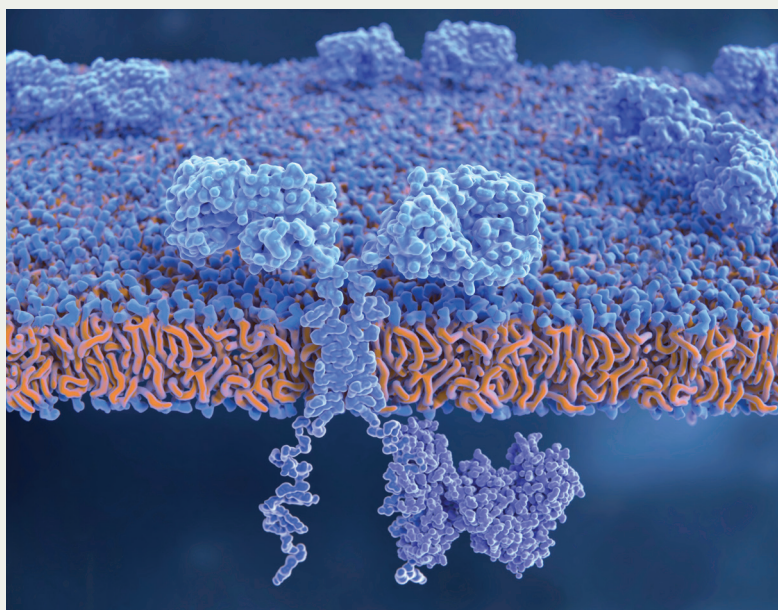
All rights reserved

Rx ONLY  
PM-US-YON-0313





# IN THIS ISSUE



## 488 **HEMATOLOGIC MALIGNANCIES: Cover** **Hitting a New Target in Multiple Myeloma**

ONCOLOGY® sat down with Sagar Lonial, MD, professor and chair of the Department of Hematology and Medical Oncology at the Emory University School of Medicine and chief medical officer at Emory's Winship Cancer Institute, to discuss BCMA-targeting agents for patients with multiple myeloma.

## 458 **Chairman's Letter** **BCMA Offers Hope in Multiple Myeloma**

Mike Hennessy Sr

## 459 **Letter to the Reader** **Use of Real-World Evidence in Hematology/ Oncology Treatment Optimization**

Julie M. Vose, MD, MBA

## 460 **GU CANCER: Clinical Update** **Incidence of Metastatic Prostate Cancer On the Rise**

Jason M. Broderick

[cancernetwork.com](http://cancernetwork.com)

Visit CancerNetwork.com, home of the journal *ONCOLOGY®* and a web destination for oncologists seeking expert peer perspectives, podcasts, and other clinically practical features.

### NEWS

**Cabozantinib Appears to Be More Effective for Treating Advanced RCC Compared With Sunitinib**



[Cancernetwork.com/cabozantinib\\_RCC](http://Cancernetwork.com/cabozantinib_RCC)

### VIDEO

**John P. Leonard, MD, on the FDA Approval of Tazemetostat for Follicular Lymphoma**



[Cancernetwork.com/tazemetostat\\_FDA](http://Cancernetwork.com/tazemetostat_FDA)

### PODCAST

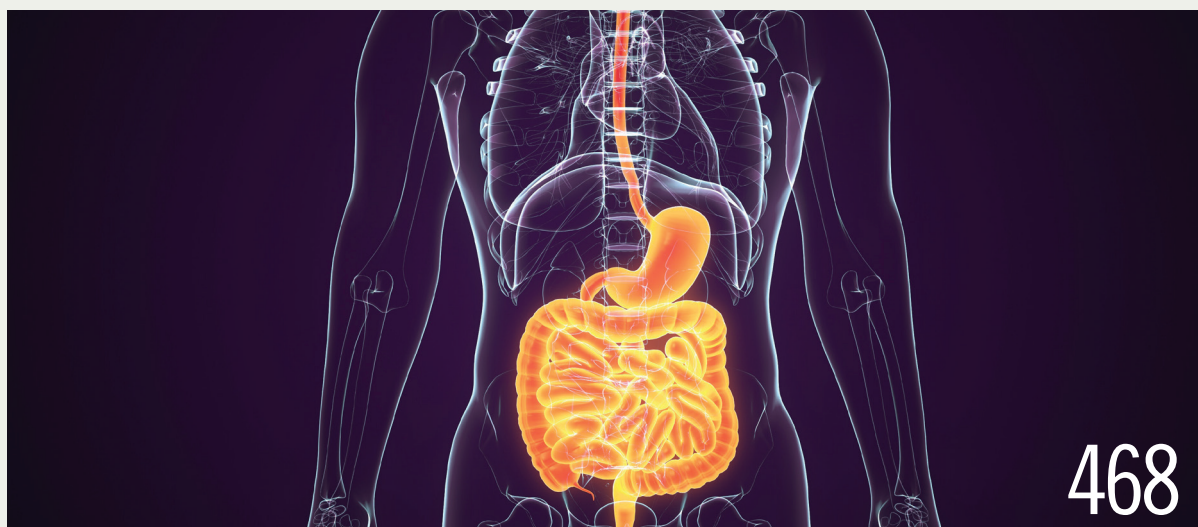
**The Psychological Aspect of Patients in Phase 1 Clinical Trials**



[Cancernetwork.com/trials\\_podcast](http://Cancernetwork.com/trials_podcast)

Table of Contents continued on page 456

# IN THIS ISSUE



468

## Clinical Trials in Progress: 462 ImmunoADAPT Trial

IMMUNE mODulation in early-stage estrogen receptor positive breast cancer treated with neoAD-juvant Avelumab, Palbociclib, and endocrine Therapy (ImmunoADAPT; NCT03573648)

## GI CANCER: Conference Abstracts 468 International Society of Gastrointestinal Oncology

## Digital Health Care: *Medical Economics*<sup>®</sup> 483 The Future of Electronic Health Records

## WOMEN'S CANCER: Pipeline 486 Updates on Key Clinical Trials and Drug Development.

## ONCOFERTILITY: Review Article 494 Supporting Decision-Making on Fertility Preservation Among Adolescent and Young Adult Women With Cancer

Jackelyn B. Payne, MPH, MA;  
Christopher R. Flowers, MD, MS;  
Pamela B. Allen, MD

Published in affiliation with



## IMMUNOTHERAPY: FDA Approval 502 FDA Approves Nivolumab Plus Ipilimumab for Previously Untreated Unresectable Malignant Pleural Mesothelioma

Kevin Wright

## LUNG CANCER: Continuing Medical Education 508 Progress and Challenges in Non-small Cell Lung Cancer and Colorectal Cancer With Pan-KRAS Inhibitors

Jonathan W. Riess, MD, MS



**THE EDITORS ARE PLEASED TO ANNOUNCE** the availability of our new parent company's continuing education activities. We've picked this one especially for our *ONCOLOGY*<sup>®</sup> readers. Go to: <https://bit.ly/2IRAKnZ>

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 claim. The publisher does not adopt any such statement or claim as its own, and any such statement or claim does not necessarily reflect the opinion of the publisher."

Advertiser and advertising agency accept and assume liability for all content (including text, representations, illustrations, opinions and facts) of advertisements printed, and also assume responsibility for any claims made against the publisher arising from or related to such advertisements. In the event that legal action or a claim is made against the publisher arising from or related to such

advertisements, advertiser and advertising agency agree to fully defend, indemnify and hold harmless the publisher, and to pay any judgment, expenses and legal fees incurred by the publisher as a result of said legal action or claim. The publisher reserves the right to reject any advertising which he feels is not in keeping with the publication's standards.

Publisher is not liable for delays in delivery and/or non-delivery in the event of an act of God, action by any government or quasi-governmental entity, fire, flood, insurrection, riot, explosion, embargo, strikes (whether legal or illegal), labor or material shortage, transportation interruption of any kind, work slow-down, or any condition beyond the control of publisher affecting production or delivery in any manner.

*ONCOLOGY*<sup>®</sup> (ISSN 0890-9091) is published monthly by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. Annual subscription rates: US, \$199 and Canada, \$219; students and nurses, \$96; international, \$249. Single copies: \$20 each. Institutional US, \$299; Canada, \$329; international, \$375. Periodicals postage paid at Trenton, NJ and at additional mailing offices. POSTMASTER: Please send address changes to *ONCOLOGY* PO Box 457, Cranbury NJ 08512-0457, USA. Publications Mail Agreement No 40612608. Return Undeliverable Canadian Addresses to: IMEX Global Solutions, PO Box 25542 London ON N6C 6B2. Canadian G.S.T number: R-124213133RT001. Printed in U.S.A.

For address changes, please notify the Circulation Department by visiting [www.surveymonkey.com/s/subscriptions](http://www.surveymonkey.com/s/subscriptions), or by mail to *ONCOLOGY*<sup>®</sup>, © 2020 MJH Life Sciences, PO Box 457, Cranbury NJ 08512-0457. Send old address, new address and attach a copy of mail label, if possible.

# PRACTICAL, PEER-REVIEWED PERSPECTIVES ONCOLOGY®

## EDITORIAL ADVISORY BOARDS

### MISSION STATEMENT

*ONCOLOGY*® and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of *ONCOLOGY*® and CancerNetwork.com's articles and features. Focused discussions capture key clinical take-aways for application in today's time-constrained practice environment.

### EDITORS-IN-CHIEF



**Julie M. Vose, MD, MBA**  
Omaha, NE



**Howard S. Hochster, MD**  
New Brunswick, NJ

### EDITORIAL BOARD

#### TUMOR CHAIRS

##### BREAST CANCER

**Sara A. Hurvitz, MD**, Los Angeles, CA

##### GENITOURINARY CANCER

**Robert A. Figlin, MD**, Los Angeles, CA

##### GASTROINTESTINAL CANCER

**Tanios S. Bekaii-Saab, MD**, Phoenix, AZ

##### HEAD AND NECK CANCER

**Eric J. Sherman, MD**, New York, NY

##### HEMATOLOGIC MALIGNANCIES

**C. Ola Landgren, MD, PhD**, New York, NY

##### LUNG CANCER

**Joshua M. Bauml, MD**, Philadelphia, PA

#### BOARD MEMBERS

##### BREAST CANCER

**William J. Gradishar, MD, FACP**, Chicago, IL

**Tari King, MD**, Boston, MA

**Vered Stearns, MD**, Baltimore, MD

**Melinda L. Telli, MD**, Palo Alto, CA

##### CANCER SURVIVORSHIP

**Matthew J. Matasar, MD, MS**, New York, NY

##### COLORRECTAL/GASTROINTESTINAL CANCER

**Edward Chu, MD**, Pittsburgh, PA

**Mehmet Sitki Copur, MD, FACP**, Omaha, NE

**Daniel Haller, MD**, Philadelphia, PA

**John L. Marshall, MD**, Washington, DC

**Shubham Pant, MD**, Houston, TX

**Matthew B. Yurgelun, MD**, Boston, MA

**Mehmet Sitki Copur, MD, FACP**, Omaha, NE

##### GENITOURINARY CANCER

**L. Michael Glodé, MD, FACP**, Denver, CO

**Paul Mathew, MD**, Boston, MA

**Elisabeth Heath, MD, FACP**, Detroit, MI

**William Oh, MD**, New York, NY

##### GYNCOLOGIC ONCOLOGY

**Mario M. Leitao Jr, MD**, New York, NY

**Franco Muggia, MD**, New York, NY

##### HEAD AND NECK CANCER

**Apar K. Ganti, MD, MS, FACP**, Omaha, NE

##### HEALTH ECONOMICS

**Nora Janjan, MD**, Dallas, TX

##### HEMATOLOGIC MALIGNANCIES

**Danielle M. Brander, MD**, Durham, NC

**Christopher R. Flowers, MD**, Houston, TX

**Steven T. Rosen, MD**, Duarte, CA

**Naval G. Daver, MD**, Houston, TX

**Ehab L. Atallah, MD**, Milwaukee, WI

##### INFECTIOUS DISEASE

**Genovefa Papanicolaou, MD**, New York, NY

##### INTEGRATIVE ONCOLOGY

**Ting Bao, MD**, New York, NY

**Linda Carlson, PhD, RPsych**, Calgary, Alberta, Canada

##### LUNG CANCER

**David S. Ettinger, MD**, Baltimore, MD

**James L. Mulshine, MD**, Chicago, IL

**Edward S. Kim, MD**, Charlotte, NC

**Jennifer W. Carlisle, MD**, Atlanta, GA

##### MELANOMA

**Richard D. Carvajal, MD**, New York, NY

**Jason Luke, MD, FACP**, Pittsburgh, PA

##### NEURO-ONCOLOGY

**David A. Reardon, MD**, Boston, MA

**Stuart A. Grossman, MD**, Baltimore, MD

**Nicole A. Shonka, MD**, Omaha, NE

##### PEDIATRIC ONCOLOGY

**David G. Poplack, MD**, Houston, TX

**Richard A. Drachtman, MD**, New Brunswick, NJ

##### PROSTATE CANCER

**Tomasz M. Beer, MD**, Portland, OR

**E. David Crawford, MD**, Denver, CO

**Judd W. Moul, MD, FACS**, Durham, NC

##### PSYCHO-ONCOLOGY

**Daniel C. McFarland, DO**, New York, NY

**Michelle Riba, MD**, Ann Arbor, MI

##### RADIATION ONCOLOGY

**Louis Potters, MD, FACR**, Hempstead, NY

**James B. Yu, MD, MHS**, New Haven, CT

##### SARCOMA

**Kenneth Cardona, MD, FACS**, Atlanta, GA

##### SUPPORTIVE AND PALLIATIVE CARE

**Thomas J. Smith, MD, FACP**, Baltimore, MD

**N. Simon Tchekmedyian, MD**, Long Beach, CA

##### SURGICAL ONCOLOGY

**Burton L. Eisenberg, MD**, Newport Beach, CA

### INTERESTED IN SUBMITTING TO *ONCOLOGY*®?

Please contact senior editor Kevin Wright at [KWright@mjhlifesciences.com](mailto:KWright@mjhlifesciences.com) for submission guidelines or more information.

# BCMA Offers Hope in Multiple Myeloma

The prognosis and survival of patients with multiple myeloma has increased significantly with the development of monoclonal antibodies and immunomodulatory drugs. Despite improved short-term outcomes, the majority of patients relapse or become treatment resistant.

For this patient population, the emergence of B-cell maturation antigen (BCMA)-targeting has provided renewed hope, with antibody drug conjugates, and chimeric antigen T-cell therapies showing high and durable responses in recent clinical trials.

In this issue of *ONCOLOGY*®, we spoke with Sagar Lonial, MD, professor and chair of the Department of Hematology & Medical Oncology at the Emory School of Medicine, Atlanta, Georgia, and chief medical officer at Winship Cancer Institute of Emory University, about the recent FDA approval of belantamab mafodotin (Blenrep) and the rise of BCMA-targeting agents for patients with relapsed/refractory multiple myeloma.

"I think we're seeing BCMA really come to the forefront of therapy," says Lonial. "The future, to me, is really exciting, because I think it suggests that we can take diseases that are treatable diseases, and potentially cure a large fraction of them."

Also in this issue, you will read a review of decision-making on fertility preservation among adolescent and young adult women with cancer. How can we support these patient's future needs, while still providing the best care right now? Read on to find out.

Within these pages, we present the abstracts from the 17th annual meeting of the International Society of Gastrointestinal Oncology (ISGIO), with special commentary from meeting co-chairs Tanios S. Bekaii-Saab, MD, section chief for Medical Oncology in the Department of Internal Medicine at Mayo Clinic in Phoenix, Arizona, and Daniel G. Haller, MD, professor of medicine emeritus, Abramson Cancer Center at the Perelman School of Medicine at the University of Pennsylvania, in Philadelphia. Also featured is a discussion of the FDA's recent approval of nivolumab (Opdivo) plus ipilimumab (Yervoy) for the treatment of patients with previously untreated unresectable malignant pleural mesothelioma. This approval marks the first new treatment option for patients with mesothelioma in over 15 years, and was desperately needed for so many patients.

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™

PRACTICAL, PEER-REVIEWED PERSPECTIVES  
**ONCOLOGY**

NOVEMBER 2020 • VOL. 34 • NO. 11

## EDITORIAL

KRISTIE L. KAHL Editorial Director

KEVIN WRIGHT Senior Editor

HANNAH SLATER Assistant Editor

MATTHEW FOWLER Assistant Editor

JENNIFER POTASH Copy Chief

RACHELLE LALIBERTE, PAUL SILVERMAN Copy Supervisors

CHENEY BALTZ, GEORGINA CARSON, REBEKAH HARRISON,  
KIRSTY MACKAY  
Copy Editors

## DESIGN & PRODUCTION

ROBERT MCGARR Creative Director

KRISTEN MORABITO Art Director

RACHEL KEATLEY Graphic Designer

JONATHAN SEVERN Circulation Director

KEYONNA GRAHAM Production Director

## PUBLISHING & SALES

BRIAN HAUG Executive Vice President  
609-325-4780 • bhaug@mmhgroup.com

MICHELLE JANIN Director of Sales  
732-429-4316 • mjanin@mmhgroup.com

RYAN HALL National Accounts Manager  
609-813-3081 • rhall@mjlifesciences.com

PATRIC PASTORE National Accounts Associate  
609-955-1694 • ppastore@mjlifesciences.com

## AUDIENCE DEVELOPMENT

KELLY KEMPER Audience Development Manager

## CORPORATE

MIKE HENNESSY SR Chairman & Founder

JACK LEPPING Vice Chairman

MIKE HENNESSY JR President & CEO

NEIL GLASSER, CPA/CFE Chief Financial Officer

MICHAEL BAER Chief Marketing Officer

TOM TOLVÉ Executive Vice President, Operations

JOE PETROZIELLO Executive Vice President, Global  
Medical Affairs and Corporate Development

SILAS INMAN Senior Vice President, Content

JOHN MORICONE Senior Vice President, I.T. & Enterprise  
Systems

SHARI LUNDENBERG Vice President, Human Resources &  
Administration

CHRIS HENNESSY Vice President, Mergers & Acquisitions

JEFF BROWN Executive Creative Director, Creative  
Services

## SUBSCRIPTIONS

888-527-7008

AN **MJH** life sciences™ BRAND

MJH Life Sciences, LLC | 2 Clarke Dr. Suite 100, Cranbury, NJ 08512 | (609) 716-7777



# Use of Real-World Evidence in Hematology/Oncology Treatment Optimization

Julie M. Vose, MD, MBA  
Neumann M. and Mildred E. Harris Professor  
Chief, Hematology/Oncology Division  
University of Nebraska Medical Center  
Buffett Cancer Center

**R**eal-world evidence (RWE) is generated from real-world data, which can be obtained from observational data outside of the clinical research setting, and could include electronic medical records (EMRs), claims and billing data, product- or disease-based registries, as well as personal devices or health applications.<sup>1</sup> These valuable data can and have been used in support of clinical trial designs, post marketing regulations, and increasingly, pharmacoeconomic analyses. The most useful RWE involves patient level disaggregated individual data, which can be used to evaluate the safety or efficacy of an intervention and/or to identify modifiers of the treatment effects. Multivariable analyses used on large databases of patients may be developed from this type of RWE to evaluate the association of prognostic markers. Another important use for RWE is cost-effectiveness analyses of 2 or more treatments relative to their cost. This type of analysis can look at health care interventions spanning pharmaceuticals, medical devices, surgical procedures, and diagnostic technologies, as well as public health interventions. Probably the newest area of RWE is research into patient-reported outcome measures used with validation or outcomes for future trial directions.

Under the 21st Century Cures Act,<sup>2</sup> the FDA's RWE program

must evaluate the potential use of real-world data to generate evidence of product effectiveness in support of indications for drugs approved under the FD&C Act section 505(c), or to help support or satisfy post-approval study requirements. Another important area for use of real-world data is to generate hypotheses for testing in controlled trials—we use this often when we see something in a patient in clinic and then go to the database to evaluate a larger number of patients for that hypothesis. The real-world data can also be used to identify biomarkers, prognostic indicators, or to evaluate cohorts in rare diseases. In some rare diseases in hematology/oncology, a randomized controlled trial is not feasible or unethical (for example, placebo based), so supportive RWE has consisted of patient level data from chart reviews, expanded access, and other practice settings.

In addition, because many clinical trials have inclusion criteria that are so narrow, they are often not representative of the real patient population with that malignancy. Therefore, gathering RWE is very important in order to apply this to our patients. This has also led to the belief that more pragmatic trials, designed to show the real-world effectiveness of the intervention or treatment in a broader, real-world patient environment, would be of great importance.<sup>3</sup>

Why is this such an important

topic for those of us taking care of patients with cancer? We utilize this information every day when discussing various treatment options with our patients, as well as the comparison of potential toxicities and outcomes. Going forward, we all need to be mindful that the patient level data we enter into the EMR must be accurate and well maintained to help formulate the RWE needed for future analyses. In addition, we will rely on health care systems to work with the medical community to have access to deidentified data for these important analytics, which shape future hypotheses and treatments for our patients of tomorrow. As with many things in life, we must learn from the past to make a new path toward the future, including optimizing cancer treatments. ■

## REFERENCES

1. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297. doi: 10.1056/NEJMs1609216
2. Compilation of the Social Security laws. 21st Century Cures Act. Pub L No. 114-255, 130 Stat. 1033. Accessed October 26, 2020. [https://www.ssa.gov/OP\\_Home/comp2/F114-255.html#:~:text=An%20Act%20to%20accelerate%20the,%E2%80%9C21st%20Century%20Cures%20Act%E2%80%9D](https://www.ssa.gov/OP_Home/comp2/F114-255.html#:~:text=An%20Act%20to%20accelerate%20the,%E2%80%9C21st%20Century%20Cures%20Act%E2%80%9D)
3. Ford I, Norrie J. Pragmatic trials. *N Engl J Med*. 2016;375(5):454-463. doi: 10.1056/NEJMra1510059

# Incidence of Metastatic Prostate Cancer On the Rise

Jason M. Broderick

**T**he incidence of metastatic prostate cancer (mPC) in the United States has been rising over the past decade, according to an analysis published in the CDC's *Morbidity and Mortality Weekly Report*.<sup>1</sup>

Although the overall age-adjusted incidence of prostate cancer went down from 155 to 105 per 100,000 men between 2003 and 2017, the CDC analysis indicated that the percentage of patients diagnosed with mPC increased from 4% to 8% during the same time period.

The CDC report examined data from the population-based cancer registries that are used for the official US Cancer Statistics composite. In total, there were 3,087,800 new prostate cancer cases diagnosed in the United States between 2003 and 2017. The incidence was highest among men aged 70 to 74 years and among Black men. The vast majority of these cases were localized (77%), followed by regional (11%), metastatic (5%), and unknown (7%). Compared with all other races/ethnicities, White men had the lowest rates of metastatic (5%) and unknown stage (6%) disease at diagnosis.

"Although approximately three-fourths of US men with prostate cancer have localized stage at diagnosis, an increasing number and percentage of men have received diagnoses of distant stage prostate cancer," noted the investigators. "Survival with distant stage prostate cancer has improved, but fewer than one-third of men survive 5 years

after diagnosis."

Survival data available for 3,104,380 men across all disease stages showed that between 2001 and 2016, the 5-year and 10-year relative survival rates (RSRs) were 97.6% and 97.2%, respectively. The 10-year RSRs for men with localized disease vs mPC were 100% vs 18.5%, respectively. The 10-year RSRs were 96.1% for patients with regional disease and 78.1% for patients whose disease status was unknown.

According to the investigators, a possible explanation for the recent uptick in the incidence of mPC was the US Preventive Services Task Force (USPSTF) issuing a grade D recommendation in 2012 against the use of prostate-specific antigen (PSA) screening in the general US population, regardless of age.

"This recommendation likely contributed to a decrease in overall reported prostate cancer incidence and might have contributed to an increase in the percentage and incidence of distant stage prostate cancer," they wrote.

The current recommended PSA screening policy has since changed slightly, with the USPSTF issuing a grade C recommendation for men aged 55 to 69 years. For this population, an individual decision on screening should be made based on a physician-patient discussion of the potential benefits and risks. Some urologists still disagree with this recommendation, however, believing that all healthy men should undergo some form of PSA screening.<sup>2</sup>

Of note, when comparing the 5-year

RSRs for 2001-2005 vs 2011-2016, the rate improved from 28.7% to 32.3% in patients with mPC. The investigators suggested that the improvement might be attributed to recent advances in the prostate cancer armamentarium, including novel antibody and hormone treatments.

Although the 5-year RSR was higher for White vs Black or Hispanic men when combining all stages of prostate cancer, the 5-year RSR for patients with mPC was higher for Black and Hispanic men compared with White men. The 5-year RSR by race for men diagnosed with mPC between 2001 and 2016 were 42.0% for Asian/Pacific Islander men; 37.2% for Hispanic men; 32.2% for American Indian/Alaska Native men; 31.6% for Black men; and 29.1% for White men.

In their concluding remarks, the CDC investigators wrote, "Understanding incidence and long-term survival by stage, race/ethnicity, and age could inform messaging related to the possible benefits and harms of prostate cancer screening and could guide public health planning related to treatment and survivor care. Further research is needed to examine how social determinants of health affect prostate cancer diagnosis and treatment; findings should inform interventions to decrease disparities in outcomes."■

**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.

➤ For full reference list, visit [cancernetwork.com/mPC\\_incidence](http://cancernetwork.com/mPC_incidence)





# Essential Resources for Multiple Myeloma

Though relatively uncommon, multiple myeloma carries no less of an impact to patients, families and caregivers. Explore and bookmark this *Cancer Network*® provider toolkit and stay connected to the most up-to-date, authoritative and essential resources.

## Read More

[cancernetwork.com/toolkits/multiple-myeloma](https://cancernetwork.com/toolkits/multiple-myeloma)



cancernetwork®

# CLINICAL TRIALS IN PROGRESS

## IMMUNOADAPT TRIAL

**TITLE:** IMMUNe mOdulation in early-stage estrogen receptor positive breast cancer treated with neoADjuvant Avelumab, Palbociclib, and endocrine Therapy (ImmunoADAPT; NCT03573648)

**BACKGROUND:** Breast cancer is the most common nondermatologic cancer in women in the United States each year. Estrogen receptor (ER)-positive breast cancer is the most common subtype, diagnosed in about two-thirds of women. While many patients with early-stage disease can experience cure, recurrence can still occur and metastatic disease is not curable; therefore, novel therapies are needed.

CDK4/6 inhibitors can arrest estrogen-mediated cell cycle growth and are synergistic when combined with endocrine therapies. Indeed, in the metastatic setting, CDK4/6 inhibitors can substantially improve progression-free survival and even overall survival; however, their benefit in early-stage disease appears to be more limited and less well defined. Recent studies demonstrated that CDK4/6 inhibitors affect antigen presentation machinery and activate T cells, suggesting that part of their mechanism of action may be due to immune modulation.

Inhibitors against PD-1 and PD-L1 have revolutionized therapy in some types of cancers; patients who respond can often experience a durable response and improved survival. While PD-L1 inhibitors are approved for patients with certain types of breast cancer, experience

to date demonstrates their limited efficacy in patients with ER-positive disease. Increasing the sensitivity to immunotherapy in ER-positive breast cancer is crucial to improve responses.

We therefore designed a phase 2 clinical trial of neoadjuvant endocrine therapy (tamoxifen with ovarian suppression for premenopausal women, and letrozole (Femara) for postmenopausal women) and avelumab (Bavencio) (PD-L1 inhibitor) with or without palbociclib (Ibrance) (CDK4/6 inhibitor) to evaluate responses and learn about the changes to the tumor microenvironment to help identify responders and understand resistance mechanisms.

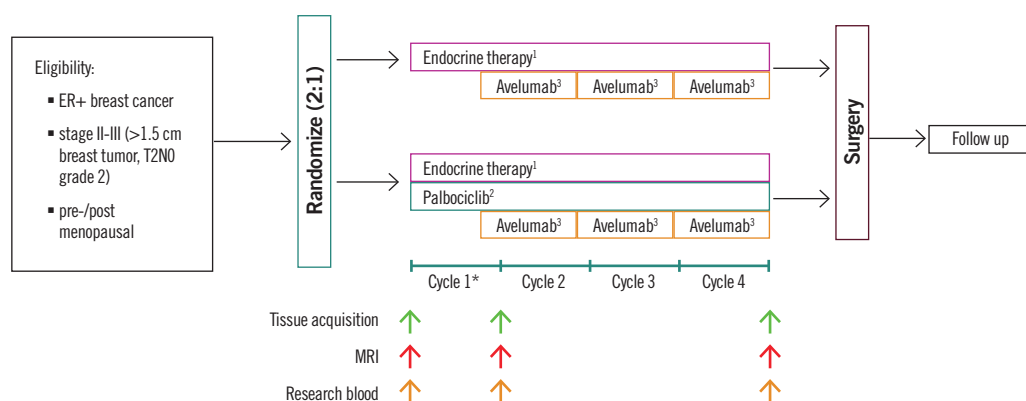
**INCLUSION CRITERIA:** Men and women (pre- or postmenopausal) with clinical stage II-III, ER-positive, HER2-negative breast cancer are eligible. Tumors must be evaluable (either by clinical exam or ultrasound). T1N+ tumors must measure at least 1.5 cm; T2N0 must be grade 2. Patients must be eligible for neoadjuvant endocrine therapy—namely, must not have endocrine insensitive disease (ie, progesterone receptor-negative, high grade/Ki67, high gene expression profile [ie, Oncotype Dx or Mammprint], clinically aggressive presentation). Patients must have a performance status of at least 1 and be aged at least 18 years. Adequate organ and bone marrow function is required (hemoglobin  $\geq$  9 g/dL; absolute neutrophil count  $\geq$  1500/mcL; platelets  $\geq$  100,000/mcL; total

bilirubin within normal institutional limits; liver function enzymes  $\leq$  2.5x institutional upper limit of normal; creatinine clearance  $>$  40mL/min by Cockcroft Gault). Patients with metastatic or inflammatory breast cancer are excluded. Use of selective serotonin reuptake inhibitors for premenopausal women (who would be receiving tamoxifen) is excluded. Use of other investigational agents and recent immunosuppressive medication use is excluded. Patients may not have had a prior diagnosis of cancer if it has been less than 3 years since their last treatment (with the exception of squamous cell carcinoma or basal cell carcinoma of the skin or cervical intraepithelial neoplasia). A personal history of breast cancer within the last 10 years is also excluded. Patients are excluded if they have autoimmune disease (except vitiligo, alopecia, stable hypothyroidism, and psoriasis not requiring systemic therapy) or uncontrolled intercurrent medical illness.

### PATIENT ACCRUAL INFORMATION

- Accrual goal: 30
- Percent accrued: 30% accrual completed. 21 slots remaining.

**STUDY SITES:** Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD; DC), Allegheny Health Network Cancer Center (Pittsburgh, PA), University of Alabama O'Neal Comprehensive Cancer Center (Birmingham, AL)



\*1 cycle = 28 days

<sup>1</sup>Tamoxifen, for premenopausal patients: 20 mg by mouth daily, days 1-28, for cycles 1-4, with gonadotropin-releasing hormone agonist on day 1 for cycles 1-4 (leuprolide intramuscular 3.75 mg or goserelin subcutaneous 3.6 mg); letrozole, for postmenopausal patients: 2.5 mg by mouth daily, days 1-28, cycles 1-4.

<sup>2</sup>Palbociclib by mouth days 1-21 for cycles 1-4.

<sup>3</sup>Avelumab days 1 and 15 for cycles 2-4.

### Co-principal investigators:

**Cesar A. Santa-Maria, MD, MSCI**

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 201 North Broadway, Rm 10262, Baltimore, MD 21287  
Tel: 410-955-8893, Fax: 410-614-9421, HopkinsBreastTrials@jhmi.edu





# BLENREP

belantamab  
mafodotin-blmf  
for injection 100 mg

## NOW APPROVED

**Please see following pages for Brief Summary of full Prescribing Information, including BOXED WARNING**

Trademarks are owned by or licensed to the GSK group of companies.

©2020 GSK or licensor.  
BLMJRNA200002 August 2020  
Produced in USA.

**Learn more today at  
[BLENREPHCP.com](https://www.blenrephcp.com)**



## BRIEF SUMMARY

# BLENREP

## (belantamab mafodotin-blmf) for injection, for intravenous use

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

### WARNING: OCULAR TOXICITY

**BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].**

**Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].**

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

## 1 INDICATIONS AND USAGE

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

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLENREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

### 2.2 Recommended Dosage

The recommended dosage of BLENREP is 2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.

### 2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:

- BLENREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLENREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

#### Corneal Adverse Reactions

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 [see Warnings and Precautions (5.1)]. Determine the recommended dosage modification of BLENREP based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity (KVA) scale.

**Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale**

Corneal Adverse Reaction	Recommended Dosage Modifications
<b>Grade 1</b> <i>Corneal examination finding(s):</i> Mild superficial keratopathy <sup>a</sup>  <i>Change in BCVA<sup>b</sup>:</i> Decline from baseline of 1 line on Snellen Visual Acuity	Continue treatment at current dose.
<b>Grade 2</b> <i>Corneal examination finding(s):</i> Moderate superficial keratopathy <sup>c</sup>  <i>Change in BCVA<sup>b</sup>:</i> Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200	Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at same dose.

**Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale (continued)**

<b>Grade 3</b> <i>Corneal examination finding(s):</i> Severe superficial keratopathy <sup>d</sup>  <i>Change in BCVA<sup>b</sup>:</i> Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200	Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.
<b>Grade 4</b> <i>Corneal examination finding(s):</i> Corneal epithelial defect <sup>e</sup>  <i>Change in BCVA<sup>b</sup>:</i> Snellen Visual Acuity worse than 20/200	Consider permanent discontinuation of BLENREP. If continuing treatment, withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.

<sup>a</sup> Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

<sup>b</sup> Changes in visual acuity due to treatment-related corneal findings.

<sup>c</sup> Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

<sup>d</sup> Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

<sup>e</sup> Corneal epithelial defect such as corneal ulcers.

#### Other Adverse Reactions

The recommended dosage modifications for other adverse reactions are provided in Table 2.

**Table 2. Dosage Modifications for Other Adverse Reactions**

Adverse Reaction	Severity	Recommended Dosage Modifications
Thrombocytopenia [see Warnings and Precautions (5.3)]	Platelet count 25,000 to less than 50,000/mcL	Consider withholding BLENREP and/or reducing the dose of BLENREP.
	Platelet count less than 25,000/mcL	Withhold BLENREP until platelet count improves to Grade 3 or better. Consider resuming at a reduced dose.
Infusion-related reactions [see Warnings and Precautions (5.4)]	Grade 2 (moderate) or Grade 3 (severe)	Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.
	Grade 4 (life-threatening)	Permanently discontinue BLENREP and provide emergency care.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3	Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.
	Grade 4	Consider permanent discontinuation of BLENREP. If continuing treatment, withhold BLENREP until improvement to Grade 1 or better and resume at reduced dose.

### 2.4 Preparation and Administration

BLENREP is a hazardous drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

Calculate the dose (mg), total volume (mL) of solution required, and the number of vials of BLENREP needed based on the patient's actual body weight. More than 1 vial may be needed for a full dose. Do not round down for partial vials.

#### Reconstitution

- Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).
- Reconstitute each 100-mg vial of BLENREP with 2 mL of Sterile Water for Injection, USP, to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. **Do not shake.**
- If the reconstituted solution is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) or at room temperature (68°F to 77°F [20°C to 25°C]) for up to 4 hours in the original container. Discard if not diluted within 4 hours. Do not freeze.

(continued on next page)

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to opalescent, colorless to yellow to brown liquid. Discard if extraneous particulate matter is observed.

#### Dilution

- Withdraw the calculated volume of BLENREP from the appropriate number of vials and dilute in a 250-mL infusion bag of 0.9% Sodium Chloride Injection, USP, to a final concentration of 0.2 mg/mL to 2 mg/mL. The infusion bags must be made of polyvinylchloride (PVC) or polyolefin (PO).
- Mix the diluted solution by gentle inversion. **Do not shake.**
- Discard any unused reconstituted solution of BLENREP left in the vial(s).
- If the diluted infusion solution is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) for up to 24 hours. **Do not freeze.** Once removed from refrigeration, administer the diluted infusion solution of BLENREP within 6 hours (including infusion time).
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted infusion solution should be clear and colorless. Discard if particulate matter is observed.

#### Administration

- If refrigerated, allow the diluted infusion solution to equilibrate to room temperature (68°F to 77°F [20°C to 25°C]) prior to administration. Diluted infusion solution may be kept at room temperature for no more than 6 hours (including infusion time).
- Administer by intravenous infusion over approximately 30 minutes using an infusion set made of polyvinyl chloride (PVC) or polyolefin (PO).
- Filtration of the diluted solution is not required; however, if the diluted solution is filtered, use a polyethersulfone (PES)-based filter (0.2 micron).

Do not mix or administer BLENREP as an infusion with other products. The product does not contain a preservative.

#### **4 CONTRAINDICATIONS**

None.

#### **5 WARNINGS AND PRECAUTIONS**

##### **5.1 Ocular Toxicity**

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

##### Keratopathy

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

##### Visual Acuity Changes

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

##### Monitoring and Patient Instruction

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

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

##### *Administration* (2.1)].

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

BLENREP is only available through a restricted program under a REMS [see *Warnings and Precautions* (5.2)].

#### **5.2 BLENREP REMS**

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

Notable requirements of the BLENREP REMS include the following:

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

Further information is available, at [www.BLENREPREMS.com](http://www.BLENREPREMS.com) and 1-855-209-9188.

#### **5.3 Thrombocytopenia**

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see *Adverse Reactions* (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

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

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

#### **5.4 Infusion-Related Reactions**

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

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

#### **5.5 Embryo-Fetal Toxicity**

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

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

#### **6 ADVERSE REACTIONS**

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

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

#### **6.1 Clinical Trials Experience**

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

The pooled safety population described in *Warnings and Precautions* reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

**Relapsed or Refractory Multiple Myeloma**

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

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

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

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

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

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

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

**Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2**

Adverse Reactions	BLENREP N = 95	
	All Grades (%)	Grade 3-4 (%)
<b>Eye disorders</b>		
Keratopathy <sup>a</sup>	71	44
Decreased visual acuity <sup>b</sup>	53	28
Blurred vision <sup>c</sup>	22	4
Dry eyes <sup>d</sup>	14	1
<b>Gastrointestinal disorders</b>		
Nausea	24	0
Constipation	13	0
Diarrhea	13	1
<b>General disorders and administration site conditions</b>		
Pyrexia	22	3
Fatigue <sup>e</sup>	20	2
<b>Procedural complications</b>		
Infusion-related reactions <sup>f</sup>	21	3
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	12	0
Back pain	11	2
<b>Metabolic and nutritional disorders</b>		
Decreased appetite	12	0
<b>Infections</b>		
Upper respiratory tract infection <sup>g</sup>	11	0

<sup>a</sup> Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

<sup>b</sup> Visual acuity changes were determined upon eye examination.

<sup>c</sup> Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

<sup>d</sup> Dry eyes included dry eye, ocular discomfort, and eye pruritus.

<sup>e</sup> Fatigue included fatigue and asthenia.

<sup>f</sup> Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

<sup>g</sup> Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

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

*Eye Disorders:* Photophobia, eye irritation, infective keratitis, ulcerative keratitis.

*Gastrointestinal Disorders:* Vomiting.

*Infections:* Pneumonia.

*Investigations:* Albuminuria.

Table 4 summarizes the laboratory abnormalities in DREAMM-2.

**Table 4. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2**

Laboratory Abnormality	BLENREP N = 95	
	All Grades (%)	Grades 3-4 (%)
<b>Hematology</b>		
Platelets decreased	62	21
Lymphocytes decreased	49	22
Hemoglobin decreased	32	18
Neutrophils decreased	28	9
<b>Chemistry</b>		
Aspartate aminotransferase increased	57	2
Albumin decreased	43	4
Glucose increased	38	3
Creatinine increased	28	5
Alkaline phosphatase increased	26	1
Gamma-glutamyl transferase increased	25	5
Creatinine phosphokinase increased	22	1
Sodium decreased	21	2
Potassium decreased	20	2

## 6.2 Immunogenicity

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

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

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

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

#### Data

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



## 8.2 Lactation

### Risk Summary

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

## 8.3 Females and Males of Reproductive Potential

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

### Pregnancy Testing

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

### Contraception

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

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

### Infertility

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

## 8.4 Pediatric Use

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

## 8.5 Geriatric Use

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

## 8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73m<sup>2</sup> as estimated by the Modification of Diet in Renal Disease [MDRD] equation) [see *Clinical Pharmacology* (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m<sup>2</sup> not on dialysis or requiring dialysis [see *Clinical Pharmacology* (12.3) of full Prescribing Information].

## 8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin 1 to ≤1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see *Clinical Pharmacology* (12.3) of full Prescribing Information].

## 15 REFERENCES

1. "OSHA Hazardous Drugs." *OSHA*. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

## 17 PATIENT COUNSELING INFORMATION

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

### Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP [see *Warnings and Precautions* (5.1)].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.1)].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see *Warnings and Precautions* (5.1)].

## BLENREP REMS

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

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see *Warnings and Precautions* (5.1)].

### Thrombocytopenia

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

### Infusion-Related Reactions

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

### Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.1, 8.3)].
- Advise women of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose [see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.3)].
- Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see *Use in Specific Populations* (8.3), *Nonclinical Toxicology* (13.1) of full Prescribing Information].

### Lactation

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

### Infertility

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

Trademarks are owned by or licensed to the GSK group of companies.

Manufactured by:

GlaxoSmithKline Intellectual Property Development Ltd. England  
Brentford, Middlesex, UK TW8 9GS  
U.S. License No. 2148

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

For:



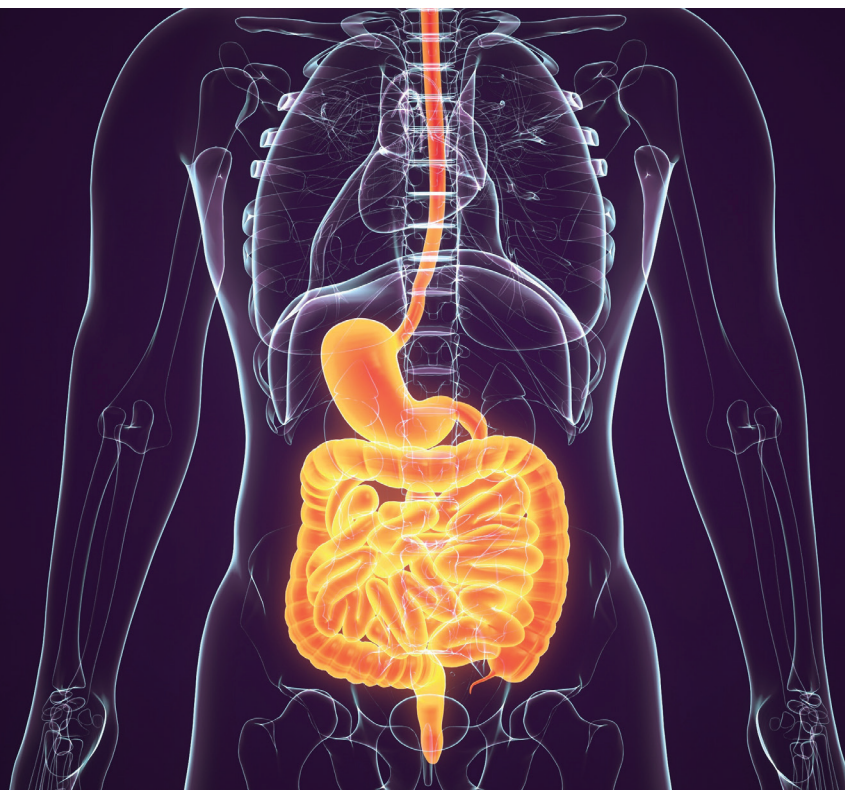
GlaxoSmithKline  
Research Triangle Park, NC 27709  
©2020 GSK group of companies or its licensor.

August 2020 BRP:1BRS

©2020 GSK or licensor.  
BLMJRNA200002 August 2020  
Produced in USA.

The BLENREP logo, featuring a stylized blue 'B' icon to the left of the text "BLENREP" in a bold, sans-serif font. Below "BLENREP" is the text "belantamab mafodotin-blmf" in a smaller, lowercase font, followed by "for injection 100 mg" in an even smaller font.

**BLENREP**  
belantamab  
mafodotin-blmf  
for injection 100 mg



## INTERNATIONAL SOCIETY OF GASTROINTESTINAL ONCOLOGY (ISGIO)

**THE 17TH ANNUAL MEETING** of the International Society of Gastrointestinal Oncology (ISGIO) was held as a 2-day virtual event on October 2-3, 2020. This multidisciplinary educational conference is dedicated to presenting and discussing some of the latest advances in the field of gastrointestinal cancer research.

**ONCOLOGY®** sat down with the co-chairs of the conference, Tanios S. Bekaii-Saab, MD, section chief for Medical Oncology in the Department of Internal Medicine at Mayo Clinic in Phoenix, Arizona, and Daniel G. Haller, MD, professor of medicine emer-

itus, Abramson Cancer Center at the Perelman School of Medicine at the University of Pennsylvania, in Philadelphia, to discuss the abstracts that were presented, and the role of the conference itself.

Bekaii-Saab noted that the conference has taken on a “GI year in review” role and has become one of the premier GI cancer meetings.

“I think another thing is that ‘bigness’ is not always great,” said Haller. “I think people can get tired of ASCO and ESMO, with them being so large. I think one of the nice things here is that

[when we’re in person] the fact that the audience can mingle with the experts and not necessarily have to see them from far away. So, the intimacy and the ability to have those one on ones, that’s always been one of the selling points.”

“Exactly,” added Bekaii-Saab. “And, to that point, I’d say that the focus of ISGIO, essentially what it was built for, is to continue growing the next generation of GI oncologists. This is the one GI meeting in the world where junior colleagues take center stage. So, it’s a great place to mentor.”

➤ **TURN TO PAGE 469** for the ISGIO Abstracts presented at the 2020 conference

# National Clinical Trial Network Gastrointestinal Cancer Trial Mentions in Electronic Physician Resources

Elizabeth Carey, MSPH; and Amarinthia Curtis, MD

Gibbs Cancer Center and Research Institute, Spartanburg, SC

**BACKGROUND.** Physicians look to various electronic resources to aid in management of patient treatment. Although national guidelines encourage clinical trial participation for patients with cancer, it is unclear if physician-facing resources help guide physicians to appropriate trials in which to enroll their patients. If resources do not mention appropriate open clinical trials, physicians miss a major management strategy.

**METHODS.** A list of open gastrointestinal cancer trials as of July 15, 2020, was obtained from the National Clinical Trial Network (NCTN). Physician facing electronic resources including UpToDate, DynaMed, WebMD, Medscape, theMedNet, WebMD, and ClinicalKey, were queried for each trial. The long name of the trial, trial name, any abbreviation associated with the trial, and definitive type of gastrointestinal cancer characteristics qualifying for the trial were searched for

in the database. Relevant management topics within each resource were also reviewed for mention of any open trial. A spreadsheet was constructed and trial mentions were tabulated.

**RESULTS.** The 23 trials were found mentioned 12 times across all 6 resources. This resulted in clinical trials being mentioned an average of 9% in each resource, with a range of 0% to 30%. A total of 30% of open NCTN gastrointestinal trials were

TABLE. Mentions of Trials Within Physician Facing Electronics Resources

Trial	Up to date	DynaMed	WebMD	MedScape	MedNet	ClinicalKey
EA2174	No	No	No	No	No	No
NRG-GI007	No	No	No	No	No	No
EA2183	No	No	No	No	Yes	No
NRG-GI006	No	No	No	Yes	No	No
S1922	No	No	No	No	No	No
A021502 (ATOMIC)	No	No	No	No	Yes	No
NRG-GI004 (COMMIT)	Yes	No	No	No	Yes	No
A021703 (SOLARIS)	No	No	No	No	No	Yes
NRG0GI002 (TNT)	No	No	No	No	Yes	No
EA2182 (DECREASE)	No	No	No	No	No	No
EA2165	No	No	No	No	Yes	No
EA2186 (GIANT)	No	No	No	No	No	No
A021806	No	No	No	No	No	No
S1815	No	No	No	No	No	No
EA2187	No	No	No	No	No	No
NRG-GI003	No	No	No	No	Yes	No
RTOG-1112	No	No	No	No	Yes	Yes
EA2142	Yes	No	No	No	No	No
A02162 (CABINET)	No	No	No	No	No	No
EAY131 (MATCH)	No	No	No	No	No	No
S1609 (DART)	No	No	No	No	No	No
Percent mentioned	9%	0%	0%	4%	30%	9%

mentioned on the MedNet, the highest of any platform. No trials were mentioned on DynaMed and WebMD. Clinical trial mentions did not always correlate with recommendation of enrollment or promotion of participation in the trial. The majority of mentions were found by searching the specific trial name.

**CONCLUSION.** Participation in clinical trials is almost always advised for patients

with cancer. However, access to open trial information is minimal within physician-facing electronic resources. Information on open or appropriate clinical trials rarely accompanies the recommendation for research participation. With extensive probing of physician-facing databases, open clinical trials were mentioned only 9% of the time (range of 0%-30%). The lack of exposure of open clinical trials in physician facing electronic databases

increases the difficulty of adherence to the recommendation of clinical trial enrollment as a management strategy. In addition to missing a major management strategy, the lack of representation of the trials may be a barrier to appropriate referrals. ■

**DISCLOSURES:** The authors report no relevant disclosures.

#### COMMENTARY

**Daniel G. Haller, MD** The table the authors created shows us that access to information on open clinical trials within physician sourcing resources is minimal at best, with clinical trials mentioned less than 10% of the time. I think 1 of the things that we as clinicians all need to do if we have involvement with these resources is to push for greater representation of the open clinical trials, which might be a barrier to appropriate referrals.

## Patterns of Use and Clinical Outcomes With Long-Acting Somatostatin Analogs for Neuroendocrine Tumors (NETs): A Nationwide French Retrospective Study in the Real-Life Setting

Brooke Harrow, PhD,<sup>1</sup> Xuan-Mai Truong Thanh, MD, MBA<sup>1</sup>; Maria de Zelicourt, MD<sup>2</sup>; Camille Nevoret, MS<sup>2</sup>; Francis Fagnani, PhD<sup>2</sup>; Florence Marteau, MS<sup>1</sup>; and Louis de Mestier, MD<sup>3</sup>

<sup>1</sup>Ipsen, Boulogne-Billancourt, France; <sup>2</sup>CEMKA, Bourg-La-Reine, France; <sup>3</sup>Department of Gastroenterology, Beaujon Hospital, Clichy, France

**BACKGROUND.** Lanreotide autogel/depot (LAN) and octreotide long-acting release (OCT) are long-acting somatostatin analogs (LA SSAs) used to treat neuroendocrine tumors (NETs). Previous studies have shown differences in dose and persistence between these LA SSAs.<sup>1,2</sup> A recent analysis of the National System of Health Data (SNDS), a national French claims database, suggested that higher LA SSA doses and more syringes were used with OCT than LAN, translating into higher overall treatment costs for patients receiving OCT.<sup>3</sup> Here, we report further analysis aiming to explore patterns of use (dispensing and administration), as well as clinical outcomes, of first-line LAN compared with OCT in the French real-life setting.

**METHODS.** This was a retrospective analysis of LA SSA use in patients with NETs conducted in 2020 using claims data from the SNDS Database, which covers ~99% of French residents.<sup>4</sup> Patients were classified as having NETs if they had full insurance coverage for a long-term disease or a hospitalization linked to a NETs ICD-10 code. Included patients were aged 18 years or greater, initiated LAN or OCT treatment between 2009 and 2016 (indicated by no LA SSA treatment in the previous 12 months) and received at least 6 subsequent dispensing of first-line LAN or OCT during the first year of treatment. Patterns of use and clinical outcomes were compared between patients receiving LAN and OCT, including average monthly dose,

use of rescue medication (short-acting SSA), treatment persistence (proportion of patients remaining on treatment), and treatment duration (in months).

**RESULTS.** The final study population comprised 4417 patients with NETs, including 2,090 who initiated treatment with OCT and 2327 who initiated treatment with LAN. Patient characteristics were broadly similar between both treatment groups. Significantly fewer patients in the LAN group had an average monthly dose above the recommended dose compared with patients in the OCT group (3.0% vs 7.3%;  $P < .0001$ ; Chi-squared test). In the first year of treatment, patients in the LAN group had significantly lower use of rescue medication (short-acting SSA)

compared with patients in the OCT group (73/2327 [3.1%] vs 208/2090 [10.0%];  $P < .0001$ ; Chi-squared test). Patients in the LAN group showed significantly higher treatment persistence in the first year (74.5% [95% CI, 72.7%-76.2%] vs 65.6% [95% CI, 63.5%-67.6%]) through the fifth year (32.1% [95% CI, 29.6%-34.5%] vs 23.9% [95% CI, 21.8%-26.1%]), compared with patients in the OCT group. Median treatment duration was significantly longer for patients in the LAN group compared with patients in the OCT group (21 [interquartile range, 12-39] vs 19 [interquartile range, 9-40] months;  $P < .0001$ ; Mann-Whitney test).

**CONCLUSION.** LAN was associated with lower rescue medication use, greater treatment persistence and longer treatment duration than OCT. It should be

noted that this was an observational study that did not control for potential confounding factors, and results should be interpreted in light of limitations inherent to a database analysis. These results suggest potential economic and clinical advantages of LAN over OCT in the management of NETs, which should be further explored in specific studies. ■

#### REFERENCES

1. Klink AJ, Feinberg B, Yu HT, et al. Patterns of care among real-world patients with metastatic neuroendocrine tumors. *Oncologist*. 2019;24(10):1331-1339. doi:10.1634/theoncologist.2018-0798
2. Cheung WY, Feuilly M, Laforty C, et al. A real-world observational study of somatostatin analogue use and costs in Canada. *J Clin Oncol*. 2020;38(suppl 4):608. doi:10.1200/JCO.2020.38.4\_suppl

3. Fagnani F, Feuilly M, Marteau F, et al. Lanreotide autogel and octreotide LAR treatment patterns: results from a nationwide French retrospective study. Presented at: 17th Annual ENETS Conference 2020; March 11-13, 2020. Accessed September 24, 2020. <https://www.enets.org/lanreotide-autogel-and-octreotide-lar-treatment-patterns-results-from-a-nationwide-french-retrospective-study.html>

4. Scaiteux LM, Droitcourt C, Balusson F, et al. French administrative health care database (SNDS): The value of its enrichment. *Therapie*. 2019;74(2):215-223. doi:10.1016/j.therap.2018.09.072

**DISCLOSURES:** BH, XMTT, FM: employee of Ipsen; MZ, CN, MZ, FF: employee of CEMKA, which received a grant from Ipsen to analyze the SNDA database; LM: Ipsen (consulting), Novartis (consulting, research funding), Pfizer (consulting).

#### COMMENTARY

**Daniel G. Haller, MD** One of the interesting aspects of this is the real-life setting in the French system, in which 99% of the French population is covered, so they know exactly how many doses are given and there's no barrier to obtain data. What this study suggested is that the long-acting agents were more efficacious, with lower use of rescue medication needed than octreotide, which suggests potential economic benefits to this treatment pattern as well.

## Concurrent Everolimus With Hepatic Transarterial Bland Embolotherapy (Evero-Embo) in Patients With Metastatic Well-Differentiated Neuroendocrine Tumors

Fariha Siddiqui, MD; Aman Chauhan, MD; Gaby E. Gabriel, MD; Jianrong Wu, PhD; Val R. Adams, PharmD; B. Mark Evers, MD; Riham El Khouli, MD; and Lowell B. Anthony, MD

Markey Cancer Center, University of Kentucky, Lexington, KY; University of Kentucky, Lexington, KY; University of Kentucky, Division of Medical Oncology, Lexington, KY

**BACKGROUND.** Intraarterial therapies in patients with well-differentiated neuroendocrine tumors (NETs) show improved treatment responses and disease control with predictable and manageable toxicities. Systemic targeted therapies, such as everolimus (Afinitor) and sunitinib (Sutent), are commonly held 2 to 4 weeks prior to and after

procedures. Embolotherapy induces anoxic injury whereas everolimus effects cell growth, proliferation, and survival. Combining these modalities may result in effective debulking of significant hepatic disease and/or delaying progression. Safety and response rates of concurrent use of everolimus with bland hepatic transarterial

embolization (TAE) have been previously reported (ASCO 2019). Historically, bland TAE and chemoembolization have median hepatic progression-free survivals (mPFS) of about 9 and 18 months, respectively. We hypothesize that by continuing everolimus during and after bland TAE, hepatic mPFS will exceed 18 months.



**METHODS.** A review of clinical and radiographic data was conducted for all sequential patients who underwent evero-embo between September 2016 and April 2018 at the University of Kentucky Markey Cancer Center. An independent radiologist performed response evaluation criteria in solid tumors (RECIST) measurements. To be included in this study, patients were required to have had systemic everolimus for 1 month or longer prior to embolization and to be on everolimus immediately post procedure.

Patients with at least 20 months post procedure follow-up were included for mPFS analysis.

**RESULTS.** A total of 51 TAEs with concurrent systemic everolimus were performed in 34 patients with NETS. Mean objective radiographic response was  $58.0 \pm 16.5\%$  (SD). Hepatic progression, per RECIST, has not been observed. Of the 34 patients, 23 had 24 or more months of follow-up post procedure; 2 patients were censored when peptide receptor ra-

diotherapy began. A mPFS of 27 months was observed.

**CONCLUSION.** Evero-embo results in a hepatic mPFS exceeding that of bland TAE or chemoembolization. With a median follow-up of 27 months, hepatic progression has not been observed. Additional follow-up is necessary to determine the actual mPFS and median overall survival. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

#### Daniel G. Haller, MD

I think the takeaway here is that certainly embolization has a role in hepatic metastases, especially in neuroendocrine tumors. This study looked at not only the toxicity patterns for the combination, but also the response rates of evero-embo, and I think the results were very encouraging. The objective response rate was about 58%, in a single institution study in 51 patients with no progression in any of the patients. The median progression-free survival is over 2 years, which is really quite long. So, the combination is not only safe, but it seems to be effective as well.

## Analysis of DNA Damage Response Gene Alterations and Its Association With Tumor Mutational Burden in Asian Colorectal Cancer

Jun Li, MD<sup>1</sup>; Chao Song, MS<sup>2</sup>; Wanglong Deng, PhD<sup>2</sup>; Yi Lu, MS<sup>2</sup>; Xiangjing Hu, PhD<sup>2</sup>; Xiaomin Li, MS<sup>2</sup>; Wenjing Xi, MS<sup>2</sup>; Feng Tao, PhD<sup>2</sup>; Huijuan Qin, MS<sup>2</sup>; and Minqi Tian, MS<sup>2</sup>

<sup>1</sup>Colorectal Surgery Department, Affiliated Hospital/Clinical Medical College of Chengdu University, Chengdu, China; <sup>2</sup>Jiangsu Simcere Diagnostics Co., Ltd. Nanjing, China

**BACKGROUND.** Colorectal carcinoma (CRC) is 1 of the most commonly diagnosed cancers in the world. Carcinomas with DNA damage response and repair (DDR) gene alterations are always observed with higher genomic instability and further lead to higher tumor mutational burden (TMB). In addition to improving sensitivity of tumor cells to poly (ADP-ribose) polymerase inhibition, somatic DDR alterations have also been demonstrated to predict response to immune checkpoint inhibitors in patients with different cancers. However, DDR defects are not well characterized in Asian patients with colorectal cancer.

**METHODS.** We systematically analyzed

somatic alterations from 242 Asian patients with colorectal cancer to provide a comprehensive view of DDR mutations with next-generation sequencing (NGS) using a 539-gene panel, including 66 DDR genes. In addition, the correlation between DDR and TMB was assessed by the Chi-square test with significance level of  $P < 0.01$ .

**RESULTS.** In total, DDR alterations were found in 35.1% (85/242) of cases. *PRKDC* (9.1%), *ATM* (8.7%), and *BRCA2* (7.0%) were the most commonly altered DDR genes in this series, followed by *ATR* (5.4%), *MSH3* (5.4%), *MSH6* (5.0%), *POLE* (5.0%), and *RAD50* (5.0%). More than 1 DDR gene alteration was found

in 36 (14.9%) of cases. Tumor mutation burden in this cohort ranged from 0 to 344.12 muts/Mb with a median value of 4.41 muts/Mb, and the population was divided into 2 groups: high TMB (TMB-H,  $\geq 6.62$  muts/Mb) and low TMB (TMB-L,  $< 6.62$  muts/Mb) using the top quartile threshold. It was demonstrated that those tumors with DDR gene mutations showed significantly higher rates of TMB-H than the wild cases (50.6% vs 16.6%;  $P < .001$ ). Overall, 29 genes involved in the DDR pathway were confirmed to be significantly associated with TMB-H in colorectal cancer ( $P < .01$ ). In addition, high microsatellite instability (MSI-H) was observed in 4.5% (11/242) of DDR-altered CRC cases, whereas



MSI-H was not detected in DDR-wild-type (WT) cases.

**CONCLUSION.** These study results confirm that DDR defects are relatively common and occurred more frequently in TMB-H

patients than in TMB-L group, which suggests that the subgroup of CRCs with DDR mutations may have a higher likelihood of response to immunotherapy. The clinical benefit from immunotherapy of CRC patient population with the DDR

gene mutations can be validated in further clinical trials. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

**Tanios S. Bekaii-Saab, MD** This study does confirm that, overall, DNA damage repair alterations are common in colorectal cancer, and are targets worth investigating. It is interesting because there is quite a discussion around the role of DDR [DNA damage response]-targeting agents alongside immune therapy. It was also interesting to see that the DDR effects seem to occur more frequently with TMB-H [tumor mutational burden-high] than in TMB-L [low], which opens the way for examining the role, perhaps, of PARP inhibitors or other DDR-targeting agents plus immune therapies.

**Daniel G. Haller, MD** I think 1 thing you may be able to take away from this is that DDR measurements could be an additional part of an algorithm to choose patients for immunotherapy, apart from MSI [microsatellite instability]-high, TMB, or PDL-1 positivity.

## Treatment Patterns and Outcomes of Systemic Therapy for Microsatellite-Stable Metastatic Colorectal Cancer in the United States

Matthew S. Dixon, PharmD; Joe Gricar, MS; and Jin Gu, PhD

*Bristol Myers Squibb, Lawrenceville, NJ*

**BACKGROUND.** Colorectal cancer (CRC) is the third most common cancer worldwide and second most common reason for cancer-related deaths. About 50% to 60% of patients diagnosed with CRC develop metastases. Of the patients with metastatic CRC (mCRC), roughly 90% to 95% have microsatellite stability (MSS) and 5% to 10% have a high degree of microsatellite instability (MSI-H). Even though the genetic drivers of MSS mCRC are well documented, most of these alterations do not currently have effective targeted therapies. The treatment patterns of patients diagnosed with MSS mCRC have not been assessed using US real-world data and there is a need to understand the most common treatment patterns—as well as duration of treatment

(DOT)—to support the pioneering of novel treatment combinations.

**OBJECTIVES.** This study was designed to evaluate treatment patterns and DOT for patients with MSS mCRC in the US. Treatment patterns and DOT have not been assessed in this population and are needed to support pioneering of novel treatment combinations.

**METHODS.** A retrospective observational study using the Flatiron Health electronic medical records database was conducted among patients with MSS mCRC who received first-line therapy on or after January 1, 2013. Descriptive statistics were used for treatment frequencies, treatment sequences, and DOT. DOT was defined

as the time between start and end dates for therapy.

**RESULTS.** In this study, 7636 patients with MSS mCRC and first-line treatment were identified. Mean age was 62 years, 55% were male, 63% were white, 65% had stage IV disease at initial diagnosis, and 72% had an Eastern Cooperative Oncology Group score of less than 2. Among patients tested for mutations, 45% had positive *KRAS*, 5% had positive *NRAS*, and 7% had positive *BRAF*. Overall, 56% of patients subsequently received second-line treatment and 28% received third-line treatment. The most common regimen was FOLFOX plus bevacizumab (Avastin) (34%) as first-line treatment, FOLFIRI plus bevacizumab (26%) in

second line, and TAS-102 (14%) in third line. The most common sequence for first line to second line was FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab (22%) and for first line to third line was FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab followed by TAS-102 (4%). Median DOT was 5.1 months (95% CI, 5.10-5.29) in

first line, 3.7 months (95% CI, 3.68-3.94) in second line, and 3.0 months (95% CI, 2.79-3.09) in third line.

**CONCLUSION.** Patients with MSS mCRC predominantly received bevacizumab plus chemotherapy in first- and second-line treatment, with a high proportion continuing bevacizumab through progression.

There was no predominant third-line treatment regimen and median DOT was less than 3.0 months, highlighting the unmet need for more effective third-line treatment options. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

**Tanios S. Bekaii-Saab, MD** This study confirms the patterns of practice in the United States, which, unlike Europe, predominantly uses bevacizumab in addition to chemotherapy in the first line. Despite the right versus left data and the emergence of EGFR inhibitors, the United States remains the land of bevacizumab (Avastin). There could be multiple factors for that, including the rush to start treating patients before having the genomic analysis such as *RAS* mutations.

**Daniel G. Haller, MD** Certainly, the predominant use of bevacizumab is driven by the fact that half of the patients in this study showed *RAS* mutations and shouldn't get an EGFR inhibitor. The advice I offer in my lectures is to just start your baseline, backbone chemotherapy. Then, when *RAS* testing is available, start the appropriate antibody. It's not like a clinical trial, in which you have to give all treatment on day 1.

## Tumor-Informed Assessment of Molecular Residual Disease and Its Incorporation Into Practice for Patients With Early- and Advanced-Stage Colorectal Cancer (CRC-MRD Consortia)

Pashtoon M. Kasi, MD<sup>1</sup>; Farshid Dayyani, MD<sup>2</sup>; Van Morris, MD<sup>2</sup>; Scott Kopetz, MD, PhD<sup>2</sup>; Aparna Parikh, MD<sup>3</sup>; Jason S. Starr, DO<sup>4</sup>; Stacey A. Cohen, MD<sup>5</sup>; Axel Grothey, MD<sup>6</sup>; Christopher Lieu, MD<sup>7</sup>; Mark O'Hara, MD<sup>8</sup>; Kate Loranger, MS<sup>9</sup>; Laura Westbrook, MS<sup>9</sup>; Shruti Sharma, PhD<sup>9</sup>; Antony S. Tin, PhD<sup>9</sup>; Shifra Krinshpun, MS<sup>9</sup>; Nicole Hook, MS<sup>9</sup>; Bernhard Zimmermann<sup>9</sup>; Paul R. Billings, MD, PhD<sup>9</sup>; and Alexey Aleshin, MD<sup>9</sup>

<sup>1</sup>University of Iowa Healthcare, Iowa City, IA; <sup>2</sup>The University of Texas MD Anderson Cancer Center, Houston, TX; <sup>3</sup>Massachusetts General Hospital, Boston, MA; <sup>4</sup>Mayo Clinic, Jacksonville, FL; <sup>5</sup>University of Washington, Seattle, WA; <sup>6</sup>West Cancer Center, Germantown TN; <sup>7</sup>University of Colorado Comprehensive Cancer Center, Aurora, CO; <sup>8</sup>University of Pennsylvania, Philadelphia, PA; <sup>9</sup>Natera, Inc., San Carlos, CA

**BACKGROUND.** Circulating tumor DNA (ctDNA) testing (often referred to as liquid biopsies) can be used for the assessment of molecular residual disease (MRD) in patients with early-stage, advanced and/or metastatic colorectal cancer (CRC). The clinical utility of ctDNA as a noninvasive biomarker has been well established in

the literature for MRD detection and for stratifying patients based on their risk of developing relapse. Prospective evaluation of this methodology in clinical practice has been limited to date.

**METHODS.** A personalized and tumor-informed multiplex PCR assay (Signatera

16-plex bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA for MRD assessment.

We analyzed and present results from an ongoing early adopter program of ctDNA testing across the spectrum of CRC management.

**RESULTS.** Here, we present a total of 535 unique CRC patients with colon ( $n = 432$ ), rectal ( $n = 77$ ), and other lower gastrointestinal cancers ( $n = 27$ ; anal, appendiceal, small bowel). Most of the patients were male (57%;  $n = 307$ ) with an average age of 61 years. MRD positivity rates and ctDNA quantification (mean tumor molecules/mL) are shown in Table 1. ctDNA detection was significantly associated with stage of disease ( $P < .0001$ ; Chi-square: 50.94,  $df = 3$ ). Additionally, in patients with radiologically measurable active metastatic disease, ctDNA detection rate was 100%. On the contrary, patients with advanced/metastatic disease who had a partial response to treatment or no evidence of disease (NED) showed 60% and 33% ctDNA positivity, respectively. In the neoadjuvant (presurgical/pretreatment) setting, ctDNA detection was also 100% in oligometastatic CRC patients.

**CONCLUSION.** This is the first large, real-world study reporting on the results from a clinically validated MRD assay. For the first time, we delineate MRD rates and quantify ctDNA concentration in patients with early-stage, advanced, and/or metastatic CRC. We found that ctDNA detection postsurgically was significantly associated with the stage of the disease. Furthermore, we provide evidence that effective ongoing treatment in patients with CRC may be correlated with ctDNA clearance. ■

**DISCLOSURES:** PK would like to acknowledge research funding from Advanced Accelerator Applications, Array BioPharma, Bristol Myers Squibb, Celgene; consultancy/advisory board: Natera and Foundation Medicine. FD would like to

TABLE 1. MRD Rates and ctDNA Quantity in Patients With Early-stage, Advanced and metastatic CRC

Stages	MRD rates	Quantity of ctDNA (Mean tumor molecules (MTM)/mL)		
		Mean	Median	Range
Stage (I-III) CRC; n = 300				
Neoadjuvant setting	4/5 (80%)	21.04	11.69	0.24-60.55
Stage I (T1-2N0)	2/15 (13%)	2.65	2.65	0.13-5.18
Stage II (T3N0)	3/53 (5.6%)	1.63	1.74	1.33-1.84
Stage II (T4N0)	4/14 (28.6%)	136.24	0.44	0.31-543.77
Stage III, low-risk (T1-3N1)	3/32 (9.3%)	2.43	1.23	0.13-872.2
Stage III, high-risk (T4, N1-2, T Any, N2)	15/38 (39.4 %)	61.17	1.23	0.13-872.2
During adjuvant therapy	2/38 (5.2%)	1.37	1.37	0.27-2.47
Surveillance	4/103	36.65	4.76	2.29-134.8
Metastatic CRC; n = 41				
Progressive/ active disease	16/16 (100%)	203.75	7.51	0.13-2149.96
Stable disease/ partial response	9/15 (60%)	7.06	1.23	0.17-51.03
No evidence of disease	4/12 (33%)	232.07	21.41	0.62-884.83
Oligometastatic CRC; n = 93				
Neoadjuvant setting	9/9 (100%)	3045.04	36.53	0.49-27,077.71
MRD (postsurgical)	26/53 (49%)	454.15	5.61	0.11-13,274.05
During adjuvant treatment	5/15 (33%)	4.54	2.21	0.48-17.75

acknowledge research funding from AstraZeneca, Bristol Myers Squibb, Genentech, Merck. VKM would like to acknowledge research funding from Array BioPharma, Bristol-Myers Squibb, EMD Serono. SK would like to acknowledge research funding from Amgen, Array BioPharma, Biocartis, EMD Serono, Genentech/Roche, Guardant Health, Lilly, MedImmune, Novartis, Sanofi. AP would like to acknowledge research funding from Array, Bristol Myers Squibb, Celgene, Eli Lilly, Genentech, Guardant Health, Novartis Pharmaceuticals UK Ltd., Plexikon, Tesaro, Tolero Pharmaceuticals. JS would like to acknowledge

support from Celgene. SC would like to acknowledge research funding from Boston Biomedical Polaris. AG would like to acknowledge research funding from Array BioPharma, Bayer, Boston Biomedical, Daiichi Sankyo, Eisai, Genentech/Roche, Lilly, Pfizer. CL would like to acknowledge research funding from Merck. MH would like to acknowledge research funding from Bristol Myers Squibb, Celldex, Lilly, Parker Institute for Cancer Immunotherapy. KL, LW, SS, AT, SK, NH, BZ, PB, and

AA are full time employees of Natera, Inc., with stocks/options to own stock in the company.

## COMMENTARY

**Tanios S. Bekaii-Saab, MD** This continues to confirm that the presence of minimal residual disease indicates an almost certain risk of disease recurrence or progression. The study also does provide evidence that treatment may be correlated with circulating free DNA [cfDNA] clearance. But there's an important caveat here: clearing cfDNA in the more advanced setting does not necessarily lead to cure after a response. So, we have to be very careful about what that means. To put this in the big perspective, these remain observations, and until they're validated in prospective randomized trials, they should not be applied to the clinical practice.



# Serial Circulating Free DNA Testing Can Detect New Genetic Alterations in Patients Undergoing Treatment for Pancreas Cancer

Gehan Botrus MD, PhD<sup>1</sup>; Mohamad Bassam Sonbol, MD<sup>1</sup>; Leylah M. Drusbosky, PhD<sup>3</sup>; Thomas Oliver, MD<sup>1</sup>; Puneet Raman MD<sup>1</sup>; Daniel Ahn MD<sup>1</sup>; Mitesh Borad, MD<sup>1</sup>; Mody Kabir, MD<sup>2</sup>; Tanios S. Bekaii-Saab, MD<sup>1</sup>

<sup>1</sup>Mayo Clinic, Scottsdale, AZ; <sup>2</sup>Mayo Clinic, Jacksonville, FL; <sup>3</sup>Guardant Health, Inc, Redwood City, CA

**BACKGROUND.** Pancreatic ductal adenocarcinoma (PDAC) is still a challenge with poor prognosis. As the disease progresses, new genetic changes may occur leading to more aggressive and less treatment responsive cells, resulting in secondary treatment resistance. The ability to detect these changes without using invasive techniques can potentially help to identify genetic targets with therapeutic implications and more enrollments in clinical trials. In this study, we aimed to evaluate the genetic landscape of circulating free DNA (cfDNA) in PDAC patients over time.

**METHODS.** From December 2014 through October 2019, 357 samples collected from 282 patients with PDAC at Mayo Clinic underwent cfDNA testing using Guardant 360, which detects single nucleotide variants, amplifications, fusions, and specific insertion/deletion mutations in up to 73 different genes. Therapeutic

relevance (TR) was defined as possible treatments within OncoKB levels 1-3B and R1.

**RESULTS.** Among 282 patients, 40 patients had at least 2 serial samples of cfDNA at the time of diagnosis and progression, 60% (24/40) were female, and age ranged from 43 to 86 years with a median age of 66 years. In addition, tissue-based profiling was available at baseline in 28/40 (70%). *KRAS* and *TP53* were the most common gene mutations found in patients with both liquid and tissue biopsy results (42%). Overall, 23/40 (57.5%) of patients developed new genetic alterations that were captured by cfDNA during the time of progression: 7/40 (17.5%) with VUS alterations, and 16/40 (40%) with pathogenic alterations. None of these new genetic alterations were detected on the baseline tissue profiling. Therapeutically relevant alterations were seen in 12 of the 40 patients (30%), including

*EGFR* (7.5%), *PIK3CA* (5.0%), *RET* (5.0%), *MET* (5.0%), *BRCA1* (2.5%), *PDGFRA* (2.5%), *ERBB2* (2.5%), and *FGFR2* (2.5%). These patients received a second-line regimen in the form of chemotherapy upon progression, and no patient was enrolled in a clinical trial targeting these alterations/pathways.

**CONCLUSION.** In PDAC patients, serial cfDNA testing can detect new genetic alterations in 40% of patients upon progression that could potentially have therapeutic relevance in 30% of cases. All such mutations were absent on both baseline tissue and liquid biopsies, suggesting tumor evolution might be responsible for resistance mechanisms. Larger studies are needed to investigate whether such findings can translate in improvement of clinical outcomes. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

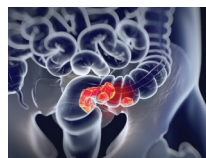
## COMMENTARY

**Daniel G. Haller, MD** This study adds to the literature looking at the evolution of alterations and appearance of mutations that, in other tumors, can be actionable. For patients who may have had serial cfDNA testing, some genetic alterations that appeared upon progression may have been suppressed, because they were very small clones, or shedding little into the circulation, but ultimately they were detected. These were mostly *KRAS* and *TP53* mutations, and they did correlate with progression of disease. Unfortunately, as most of the mutations that were reported were not actionable, the problem remains: What can we do with these findings?

cancernetwork.com™ For more great content check out our website.



**Molecular Profiling In Metastatic Colorectal Cancer**  
[cancernetwork.com/mCRC\\_podcast](http://cancernetwork.com/mCRC_podcast)



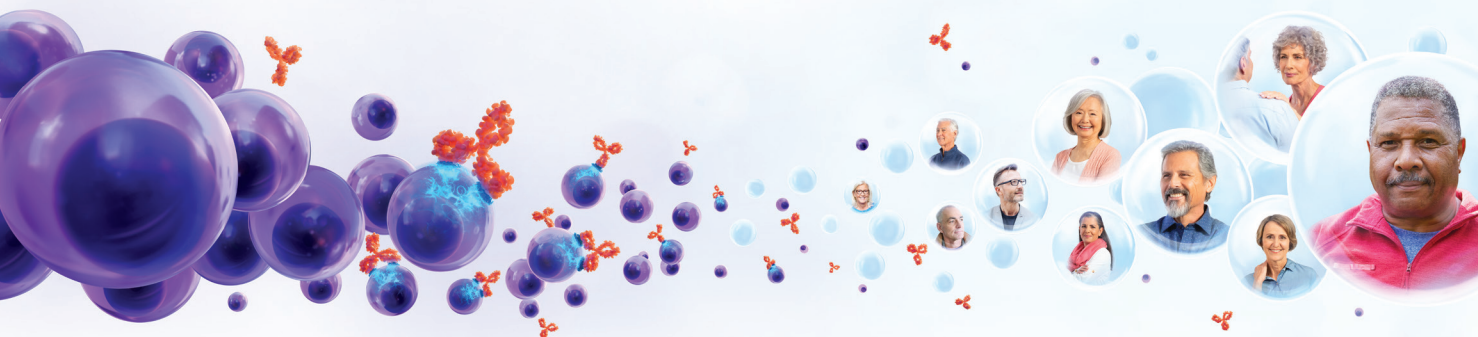
**Frontline Pembrolizumab Improves Health-Related QOL In DNA Repair-Deficient Metastatic CRC**  
[cancernetwork.com/pembrolizumab\\_crc](http://cancernetwork.com/pembrolizumab_crc)

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®).<sup>2</sup>

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.<sup>1</sup>

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.**

  
**SARCLISA®**  
(isatuximab-irfc)  
Injection for IV use | 500mg/25mL, 100mg/5mL

# 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<sup>1</sup>

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 m<sup>2</sup>), high cytogenetic risk, or a history of COPD or asthma



Who may have **poor performance status** or are  **$\geq 75$  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  $\geq 75$  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.<sup>1</sup>

**PATIENT CHARACTERISTICS:** The median patient age was 67 years (range, 36 to 86), and 20% of patients were  $\geq 75$  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 m<sup>2</sup>) 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.<sup>1</sup>

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

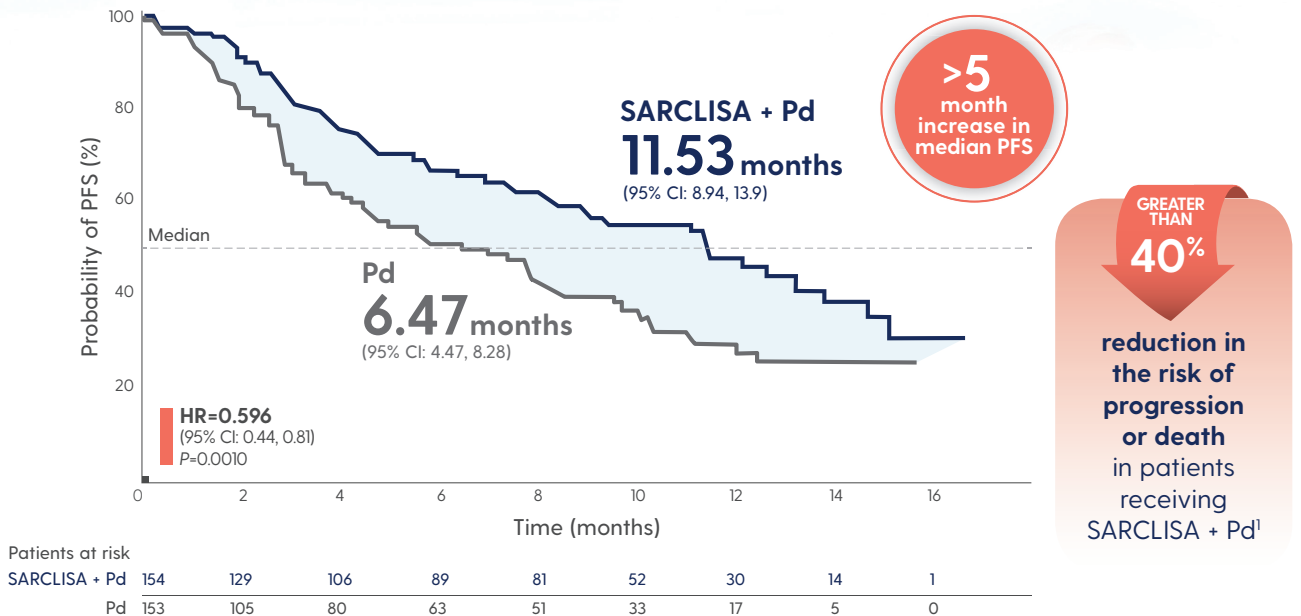
## Important Safety Information (cont'd)

### Infusion-Related Reactions (cont'd)

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

# SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone<sup>1</sup>



The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.<sup>1</sup>

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.<sup>1</sup>

SARCLISA + Pd showed a significant increase in ORR<sup>1\*</sup>

SARCLISA + Pd (n=154)		Pd (n=153)
<b>60.4%</b> ORR	<b>P&lt;0.0001</b>	<b>35.3%</b> ORR
<b>31.8%</b> ≥VGPR	<b>~4× increase</b>	<b>8.5%</b> ≥VGPR
<b>35</b> days	<b>Median time to first response among responders</b>	<b>58</b> days

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

## Important Safety Information (cont'd)

### Neutropenia

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

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.

**SARCLISA®**  
(isatuximab-irfc)  
Injection for IV use | 500 mg/25 mL, 100 mg/5 mL



# 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  $1.0 \times 10^9/L$ , 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 ( $\geq 20\%$ ) 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

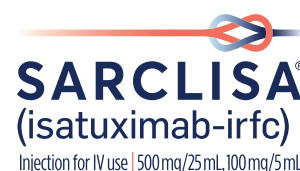
Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

**Please see accompanying brief summary of full Prescribing Information.**

**References:** 1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 9, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.



© 2020 sanofi-aventis U.S. LLC. All rights reserved. MAT-US-2015811-v2.0-09/2020



**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**

Cycle	Dosing schedule
Cycle 1	Days 1, 8, 15, and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

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 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 *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 backbone treatment, before SARCLISA and pomalidomide administration. Administer the recommended premedication agents 15 to 60 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 concerning 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 diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

**2.5 Administration**

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU])

- with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (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 infusion solution concomitantly in the same intravenous line with other agents.

**Infusion Rates**

Following dilution, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of 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**

	Dilution Volume	Initial Rate	Absence of Infusion-Related Reaction	Rate Increment	Maximum Rate
First infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/hour every 30 minutes	200 mL/hour
Subsequent infusions	250 mL	200 mL/hour	—	—	200 mL/hour

**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 most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension 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 of the initial infusion 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, as shown in Table 2 [see *Dosage and Administration* (2.5)]. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate 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). 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%) [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 delay SARCLISA dose until neutrophil count recovery to at least  $1.0 \times 10^9/L$ , and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

**5.3 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, as per International Myeloma Working Group (IMWG) guidelines.

**5.4 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 [see *Drug Interactions* (7.1)].

**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 [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 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 [see *Use in Specific Populations* (8.1, 8.3)]. 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.

**6 ADVERSE REACTIONS**

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-Related Reactions [see *Warnings and Precautions* (5.1)]
- Neutropenia [see *Warnings and Precautions* (5.2)]
- Second Primary Malignancies [see *Warnings and Precautions* (5.3)]

**6.1 Clinical Trials Experience**

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

**Multiple Myeloma**

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets  $\geq 75,000$  cells/mm<sup>3</sup>, absolute neutrophil count  $\geq 1 \times 10^9/L$ , creatinine clearance  $\geq 30$  mL/min (MDRD formula), and AST and/or ALT  $\leq 3 \times$  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 (Pd) (n=149) [see *Clinical Studies* (14) in the full prescribing information]. Among patients receiving Isa-Pd, 66% 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 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 (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%]). Permanent discontinuation due to an adverse reaction (grades 1–4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). In addition, SARCLISA alone was discontinued in 3% of patients due to infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).

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 Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial**

Adverse Reactions	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Infusion-related reaction	38	1.3	1.3	0	0	0
<b>Infections</b>						
Pneumonia*	31	22	3.3	23	16	2.7
Upper respiratory tract infection†	57	9	0	42	3.4	0
<b>Blood and lymphatic system disorders</b>						
Febrile neutropenia	12	11	1.3	2	1.3	0.7
<b>Respiratory, thoracic and mediastinal disorders</b>						
Dyspnea‡	17	5.0	0	12	1.3	0
<b>Gastrointestinal disorders</b>						
Diarrhea	26	2	–	19	0.7	–
Nausea	15	0	–	9	0	–
Vomiting	12	1.3	–	3.4	0	–

CTCAE version 4.03  
\*Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jirovecii pneumonia.  
†Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.  
‡Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the hematology laboratory abnormalities in ICARIA-MM.

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

Laboratory Parameter n (%)	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)			Pomalidomide + Dexamethasone (Pd) (N=149)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	151 (99)	48 (32)	0	145 (97)	41 (28)	0
Neutropenia	146 (96)	37 (24)	92 (61)	137 (92)	57 (38)	46 (31)
Lymphopenia	140 (92)	64 (42)	19 (13)	137 (92)	52 (35)	12 (8)
Thrombocytopenia	127 (84)	22 (14)	25 (16)	118 (79)	14 (9)	22 (15)

**Description of Selected Adverse Reactions**  
Infusion-related reactions  
In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypertension,

and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 55 minutes.  
In a separate study (TCD 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.  
Infections  
In ICARIA-MM, the incidence of Grade 3 or higher infections was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.  
**6.2 Immunogenicity**  
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other isatuximab-irfc products may be misleading.  
In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent ADAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.  
**7 DRUG INTERACTIONS**  
**7.1 Laboratory Test Interference**  
**Interference with Serological Testing**  
SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see Warnings and Precautions (5.4)].  
**Interference with Serum Protein Electrophoresis and Immunofixation Tests**  
SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria [see Warnings and Precautions (5.4)].  
**8 USE IN SPECIFIC POPULATIONS**  
**8.1 Pregnancy**  
**Risk Summary**  
SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on SARCLISA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of SARCLISA and 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. Pomalidomide is only available through a REMS program.  
**Clinical Considerations**  
**Fetal/neonatal reactions**  
Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Defer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

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

**Data**  
**Animal data**  
Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetomaternal immune tolerance (mice), and early embryonic development (frogs).  
**8.2 Lactation**  
**Risk Summary**  
There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.  
**8.3 Females and Males of Reproductive Potential**  
**Pregnancy Testing**  
With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.  
**Contraception**  
**Females**  
SARCLISA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.  
**Males**  
Refer to the pomalidomide prescribing information.  
**8.4 Pediatric Use**  
Safety and effectiveness in pediatric patients have not been established.  
**8.5 Geriatric Use**  
Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 and over, while 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years 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 or symptoms of adverse effects and take all appropriate measures immediately.

Manufactured by:  
sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807  
A SANOFI COMPANY  
U.S. License No. 1752

SARCLISA is a registered trademark of Sanofi

©2020 sanofi-aventis U.S. LLC

ISA-BPLR-SA-MAR20

Revised: March 2020



# The Future of Electronic Health Records

**T**he digitization of patient data and creation of electronic health records (EHRs) has brought about tremendous benefits for clinicians, but a lack of consistent implementation, and issues with user interface and multiplatform integration remain.

A 2018 joint study from Stanford Medicine and The Harris Poll noted that although 63% of physicians believed that EHRs generally led to improved care, 71% indicated that the implementation of EHRs led to greater physician burnout, and 59% believed the system needed a complete overhaul.<sup>1</sup>

*Medical Economics*<sup>®</sup>, a sister publication of *ONCOLOGY*<sup>®</sup>, recently spoke with Rob Tennant, director of health information technology policy at the Medical Group Management Association, about revamping the EHR system and what improvements physicians can expect to see soon.

*Note: The transcript has been edited for clarity and brevity.*

**Q:** Looking out over the next 12 months or so, do you see any major milestones in the area of interoperability for EHRs?

**TENNANT:** I think we're starting to see the regulations come out from both the Office of the National Coordinator for Health Information Technology (ONC) and the Centers for Medicare & Medicaid Services in support of the 2016 Cures Act. I think when we look at the next few months, we'll start to see things like TEFCA—the Trusted Exchange

Framework and Common Agreement regulation—which should help create the highway that allows health information exchange to occur more effectively nationwide. We're also looking at more information from both ONC and the Office of Inspector General in terms of information blocking, and certainly on the idea around enforcement, can there be additional enforcement levers placed on providers? We're also looking for the hospital requirement on admit, discharge, transfer, the ADT requirement, for that to come forward, and that has a real potential of giving practices critical data on their patients. They would know for example, if a diabetic patient of theirs ended up in the emergency department on the weekend, it would allow them to follow up with the patient on Monday morning, and make sure they don't end up back in the ED the following weekend. So, I think we're looking for the Cures Act regulations to come forward. Again, a lot of excitement, but a lot of work ahead as well.

**Q:** The number of EHR vendors has declined over the years. Do you see any activity as far as either mergers or vendors that might leave the market?

**TENNANT:** Every time the government issues new regulations, new requirements, on software developers, we start to see some vendors fall by the wayside, or we start to see some merge. It's not surprising, as it's very expensive for these companies to redevelop their products. I think we've seen some consolidation, and

I expect there to be more, candidly, because the new Cures Act regulations put a heavy burden on software developers to meet new certification requirements. And because of that, I suspect we'll see some vendors not be able to meet these new requirements. I think the challenge for practices, of course, is if their vendor of choice is not recertified to the new standard—what they're calling the 2015 Edition Cures Update—then at some point, probably in 2023, they would not be eligible to continue participating in the promoting interoperability component of MIPS (Merit-Based Incentive Payment System). So, we're going to watch that very closely, because it could have an impact on whether practices can participate in the quality reporting programs.

**Q:** There's been a lot of talk about apps and how they could improve EHRs. What's happening in that arena?

**TENNANT:** A lot. I think this has the potential—and I use that word potential—of absolutely transforming the care delivery process, both on the clinical side, and on the administrative side. I think the vision for the government, and I've seen Don Rucker, MD, (the head of ONC) literally hold up his smartphone and explain that the future of health care is exactly how we use our smartphones by using apps. All apps are avenues to data. He often uses the analogy of Travelocity or Expedia, where you want to take a flight. Your app allows you into the database of these travel booking companies



to get the information that you need. The potential for apps to do something similar in health care is very exciting. For example, on the clinical side, the HL7 International Da Vinci project folks are working on a number of use cases. One is sharing data between care settings, and it could be between laboratories and practices, between a health plan and a health plan, or between health plans and providers. The idea is that by leveraging the health care interoperability resources standards, you're able to use data at the point of care. I think that's the most exciting feature here. The idea that the practice could have apps that allow it to, for example, do a prior authorization, perhaps even in real time. The goal for us is to both decrease the volume of prior auths, but also, if it is required, to make it as easy as possible for both the practice and the patient. The idea is apps simply move data from point A to point B, and also open up doors. For example, for quality reporting for things like social determinants of health, ideally, when the practice is speaking to the patient, they would have access to drug formulary data to prior auth information, but also potentially to the local food banks, and perhaps to mental health services in the area that they could direct the patient to. The opportunities are there for the EHR to be the platform where physicians and their staff can receive and send data seamlessly. That helps the patient and of course, helps them with their practice as well. So huge opportunities, but we're not quite there yet.

**Q:** Usability has been a major complaint of doctors for many years. What are EHR vendors doing to improve the user experience?

**TENNANT:** Frankly, I've never talked to a physician who said, "Boy, I just can't wait to get on my EHR in the morning." They understand their functionality, their utility, they know how important they are. They know, in some form, the capabilities that these software programs

have. But boy, they're just not intuitive. And it goes across the board. It's not just 1 or 2 vendors. Part of the problem has been that the vendors have been focused very much on meeting government program requirements. They've spent less time working on interfaces to make the user experience for both the clinician and the administrative staff easier. Hopefully we're moving in that direction a little more. Because it's not just that the usability is a hassle, it can also bleed into the area of patient safety. If things aren't captured easily, if the information isn't presented in an effective way, it can impact patients' safety. This should be, and I think is, a priority. And we're certainly encouraging the government to work closely with the EHR vendor developers to make sure that usability is improved, and patient safety is maintained.

**Q:** As we move toward the next generation of EHRs, what are the biggest changes doctors can expect to see?

**TENNANT:** We talked about, and I'll get into something I call point of care. When you're dealing with data, really, what you want is the data at your fingertips. If I go back to the Travelocity app, if I get on it and I say, "OK, I want to know what the cost is for a flight to New York," and it gets back to me in 2 weeks, that's not helpful. At the point of care, data flow is going to be the biggest change in health care, I believe, over the next year to 2 years. For example, already there are a number of vendors that offer point-of-care solutions on the medication side. If the patient is standing, or sitting in front of the physician, and the physician says, "Well, we need to put you on medication A," they can immediately check with this software program. It pings the health plan formulary to see if it's in the formulary, it indicates whether it requires a prior authorization. It provides the patient's out-of-pocket expense, and it can provide the therapeutic alterna-

tive. If drug A is not in the formulary and requires a prior auth, it's a \$500 out-of-pocket cost for the patient. But there's a therapeutic alternative, which is in the formulary and doesn't require a prior auth, and is \$20 out of pocket, and has the same efficacy as drug A. It allows that conversation to take place with the patient immediately, rather than in the traditional approach, where the prescription is written, the patient goes to the pharmacy only to find out there that the cost is \$500. They say, "No thanks," they walk away and they don't get the medication, or they've got to make a follow-up visit to the physician to get a new script. This streamlines that process tremendously.

The question becomes, can we merge that technology with medical services? Now you want to send your patient for a particular test. Wouldn't it be nice to know immediately whether that is not only clinically appropriate through clinical decision-support technology, but also whether the health plan is going to pay for it, and what the out-of-pocket expense will be? In the future, there will be an API (application programming interface) feed that will tell the physician there are, for example, 10 MRI vendors in the area, and here are the costs out of pocket for the patient, and allow the physician to have that conversation and keep costs lower for the patient. I think the point-of-care data flow is the next exciting thing to happen, and so we're looking for that over the next few years. ■

**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

1. The Harris Poll and Stanford Medicine. How Doctors Feel About Electronic Health Records. March 2018. Accessed October 22, 2020. <http://www.med.stanford.edu/content/dam/sm/ehr/documents/EHR-Poll-Presentation.pdf>



## The latest on prostate cancer, all in one place

Prostate cancer is the most common cancer among men, after skin cancer. However, the disease can be treated successfully. Explore and bookmark this **Cancer Network® provider toolkit** and stay connected to the most up-to-date, authoritative and essential resources.

Explore now:

**[cancernetwork.com/toolkits/prostate-cancer](https://cancernetwork.com/toolkits/prostate-cancer)**

### Frontline Fulvestrant, Palbociclib Combo Is Effective for Endocrine-Sensitive, HR+/HER2- Metastatic Breast Cancer

Data from the phase 2 FLIPPER trial (GEICAM/2014-12; NCT02690480) indicated that frontline fulvestrant (Faslodex) in combination with palbociclib (Ibrance) demonstrated an improvement in progression-free survival (PFS) at 1 year compared with fulvestrant and placebo alone in patients with endocrine-sensitive hormone receptor-positive, HER2-negative metastatic breast cancer.<sup>1</sup>

The findings, which were presented at the 2020 European Society of Medical Oncology (ESMO) Virtual Congress, also demonstrated that the doublet regimen led to improvements in median PFS, objective response rate (ORR), and clinical benefit rate (CBR) compared with fulvestrant alone.

After a median follow-up of 28.6 months (range, 1.5-44.8), the PFS rate at 1 year was 83.5% with fulvestrant and palbociclib versus 71.9% with fulvestrant and placebo (HR 0.55; 80% CI, 0.36-0.83;  $P = .064$ ), meeting the trial's primary end point.

Median PFS was 31.8 months (80% CI, 30.3-33.4) with the doublet and 22 months (80% CI, 18.5-25.1) with fulvestrant alone (adjusted HR, 0.52; 80% CI, 0.39-0.68;  $P = .002$ ).

A total of 189 patients were enrolled and randomized to either the experimental arm of fulvestrant and palbociclib ( $n = 94$ ) or the control arm of fulvestrant and placebo ( $n = 95$ ). Patients were stratified by visceral versus nonvisceral metastases and metastatic de novo presentation versus recurrent presentation at study entry.

Fulvestrant was administered at 500 mg on days 1 and 15 of the first cycle and then once every 28 days thereafter. Palbociclib was given at 125 mg for 3 weeks on and 1 week off of every 28-day cycle. Treatment was given until

disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent.

Those with visceral disease who were treated with fulvestrant and palbociclib ( $n = 57$ ) had a median PFS of 30.9 months vs 19.4 months with fulvestrant and placebo ( $n = 57$ ; HR, 0.53; 80% CI, 0.38-0.73;  $P = .013$ ). At 1 year, the PFS rate was 81.8% vs 69.6% with the doublet and fulvestrant monotherapy, respectively (HR, 0.55; 80% CI, 0.33-0.92;  $P = .1397$ ).

The ORR was 68.3% in the investigational arm compared with 42.2% in the control arm (odds ratio [OR], 2.9; 80% CI, 1.79-4.62;  $P = .004$ ). The CBR, which was defined as responses plus stable disease for at least 24 weeks, was 90.4% with the combination regimen versus 80.0% with fulvestrant alone (OR, 2.3; 80% CI, 1.33-4.03;  $P = .048$ ).

Treatment-related adverse events (AEs) were observed in 89.4% of patients who received fulvestrant and palbociclib compared with 62.1% in those who received fulvestrant alone. About 15% of patients in the investigational arm discontinued palbociclib and 4.3% discontinued all study drugs whereas 4.2% in the control arm discontinued treatment. Serious AEs were reported in 26.6% of patients in the combination arm vs 20.0% in the monotherapy arm. Two on-study treatment deaths were reported in the fulvestrant and palbociclib arm, but neither were considered due to treatment.■

#### REFERENCE

1. Albanell J, Martinez MTM, Ramos M, et al. GEICAM/2014-12 (FLIPPER) study: First analysis from a randomized phase II trial of fulvestrant (F)/palbociclib (P) versus (vs.) F/placebo (PL) as first-line therapy in postmenopausal women with HR (Hormone Receptor)+/HER2- endocrine sensitive advanced breast cancer (ABC). *Ann Oncol*. 2020. 31(suppl\_4): S1142-S12-15. 10.1016/j.aanonc/annonc325

To read the full article visit:  
[cancernetwork.com/fulvestrant\\_BC](https://cancernetwork.com/fulvestrant_BC)

### Balstilimab Monotherapy, Combination Shows Promise in Recurrent/Metastatic Cervical Cancer

Results from 2 independent phase 2 trials presented during the 2020 ESMO Virtual Congress indicated that the investigative PD-1 inhibitor balstilimab (AGEN2034) demonstrated promising objective response rates (ORRs), either as a single agent or combined with the CTLA-4 inhibitor zalifrelimab (AGEN1884), in patients with recurrent or metastatic cervical cancer.<sup>1</sup>

In the modified intent-to-treat (ITT) population, treatment with single-agent balstilimab elicited a 14% ORR, which included 3 complete responses (CRs) and 20 partial responses (PRs). When patients were treated with balstilimab in combination with zalifrelimab, the ORR increased to 22%, with 8 CRs and 23 PRs. The median duration of response (DOR) for balstilimab monotherapy was 15.4 months (1.1+ to 15.4) while median DOR for the balstilimab/zalifrelimab was not reached (1.3+ to 16.6+).

The presentation follows a September 2020 announcement from the manufacturer of balstilimab, Agenus Inc., which stated that a rolling submission of a biologics license application to the FDA has been initiated for single-agent balstilimab for the treatment of patients with recurrent/metastatic cervical cancer.<sup>2</sup>

Balstilimab was administered at 3 mg/kg every 2 weeks for both trials, with zalifrelimab added at a dose of 1 mg/kg every 6 weeks (NCT03495882) for the combination study. Imaging was conducted every 6 weeks for 2 years.

The primary end point was ORR via RECIST v1.1 criteria, as assessed by an independent review committee; secondary end points were progression-free survival, overall survival, DOR, and safety.

In the single-agent trial, 161 patients comprised the safety population, and 160 were in the modified ITT population; 138 patients had received 1 or more



prior line of chemotherapy. The median age was 53 years, and 47% of patients had an ECOG performance status of 0.

In the combination trial, 155 patients were in the safety population, and 119 had received 1 or more lines of chemotherapy. A total 143 patients comprised the modified ITT population with baseline measurable disease. The median age was 50 years, and 57% of patients had an ECOG performance status of 0.

In patients who received 1 or more lines of prior chemotherapy, the ORR in the single-agent balstilimab trial was 13%, with 3 CRs and 15 PRs. For those who received the combination and prior chemotherapy, the ORR was 20%, with 6 CRs and 18 PRs.

The treatment was found to be well tolerated in both studies and no new safety signals were identified. The combination trial saw more immune-related adverse effects (irAEs) than the single-agent study. Specifically, gastrointestinal (GI) disorders occurred in 8.4% and 5.6% of the combination and monotherapy arms, respectively. Grade 3 or higher immune-related treatment-related adverse effects were GI disorders (2.6% with the combination vs 3.1% with balstilimab alone), laboratory abnormalities (3.9% vs 1.2%, respectively), and skin and subcutaneous tissue disorders (1.9% vs 0.6%).■

## REFERENCES

1. O'Malley DM, Oaknin A, Monk BJ, et al. Single-agent anti-PD-1 balstilimab or in combination with anti-CTLA-4 zifitumab for recurrent/metastatic (R/M) cervical cancer (CC): Preliminary results of two independent phase II trials. Presented at: 2020 ESMO Congress; September 19-21, 2020; virtual. Abstract LBA34.
2. Agenus initiates rolling BLA submission of balstilimab for recurrent/metastatic cervical cancer. News release. Agenus Inc. September 18, 2020. Accessed September 18, 2020. <https://investor.agenusbio.com/news-releases/news-release-details/agenus-initiates-rolling-bla-submission-balstilimab>

To read the full article visit:  
[cancernetwork.com/balstilimab\\_cc](http://cancernetwork.com/balstilimab_cc)

## Study Sees Encouraging Responses With Tisotumab Vedotin in Recurrent/Metastatic Cervical Cancer

Findings from the single-arm innovaTV 204 trial indicated that tisotumab vedotin demonstrated an objective response rate (ORR) of 24% (95% CI, 15.9%-33.3%) in patients with recurrent and/or metastatic cervical cancer who were previously treated with doublet chemotherapy and bevacizumab (Avastin), if eligible.<sup>1</sup>

The ORR, which was assessed by an independent imaging review committee (IRC), comprised a 7% complete response rate and a 17% partial response rate, and the median duration of response (DOR) was 8.3 months (95% CI, 4.2-not reached). Most responses were rapid, with a median time to response of 1.4 months (range, 1.1-5.1), and investigators noted that activity was observed within the first 2 treatment cycles.

Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and is covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker.

In the pivotal, single-arm, multicenter, phase 2 innovaTV 204 trial (NCT03438396), 101 patients with a median age of 50 years (range, 31-78) with previously treated recurrent and/or metastatic cervical cancer were given tisotumab vedotin at 2.0 mg/kg intravenously every 3 weeks until either disease progression or unacceptable toxicity. Tumor responses were assessed using CT/MRI at baseline every 6 weeks for the first 30 weeks, and then every 12 weeks thereafter.

The median duration of treatment was 4.2 months (range, 1-16), with a median 6 doses (range 1-21) of tisotumab vedotin received and a high dose intensity was observed (95.9%). Four patients had treatment ongoing, and the majority of patients discontinued therapy due to radiographic disease progression (65%), followed by adverse events (AEs; 13%),

clinical progression (8%), withdrawal of consent (5%), death (4%), and investigator decision (1%). Thirty-three percent of patients remain in follow-up for survival.

At a median follow-up of 10.0 months (range, 0.7-17.9), additional findings showed that 49% of patients achieved stable disease and 24% of patients had progressive disease; 4% of patients were not evaluable, all via IRC. Moreover, target lesions were reduced in 79% of patients with 1 or more postbaseline scan.

Clinical meaningful responses were also observed regardless of tumor histology (squamous, 23%; nonsquamous, 25%), lines of prior therapy (1, 28%; 2, 13%), responses to prior systemic treatment (responded, 26%; did not respond, 21%), and whether or not they received frontline doublet chemotherapy with bevacizumab (yes, 19%; no, 32%).

Tisotumab vedotin showcased a manageable and tolerable safety profile, with no new safety signals identified. The most common treatment-related AEs (TRAEs) with a 10% or higher incidence rate included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (24%), dry eye (23%), myalgia (15%), anemia (12%), asthenia (12%), arthralgia (12%), decreased appetite (11%), keratitis (11%), and pruritis (10%). Grade 3/4 TRAEs occurred in 28% of patients. Of the 4 patients who died, 1 was due to septic shock that was considered to be treatment related.■

## REFERENCES

1. Coleman RL, Lorusso D, Gennigens A, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer: results from the phase 2 innovaTV 204/GOG-3023/ENGOT-cx6 study. Presented at: 2020 ESMO Virtual Congress; September 19-21, 2020; Virtual. Abstract LBA32.
2. Hong DS, Concin N, Vergote I, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. *Clin Cancer Res*. 2020;26(6):1220-1228. doi:10.1158/1078-0432.CCR-19-2962

To read the full article visit:  
[cancernetwork.com/tisotumab\\_cc](http://cancernetwork.com/tisotumab_cc)



## MEET OUR EXPERT



**Lonial** is chair of the Department of Hematology and Medical Oncology at the Emory University School of Medicine and Chief Medical Officer at Winship Cancer Institute at Emory University.

## Hitting a New Target in Multiple Myeloma

‘The future, to me, is really exciting.’

The development of novel therapies including proteasome inhibitors, monoclonal antibodies, and immunomodulatory drugs have significantly improved the prognosis and survival of patients with multiple myeloma. Despite the improved outcomes, the high rate of treatment resistance and relapsed disease indicates a need for continuing therapeutic innovation.

The emergence of B-cell maturation antigen (BCMA)-targeting agents has given this patient population new hope, demonstrating promising and exciting clinical results in ongoing trials.

*ONCOLOGY*® sat down with Sagar Lonial, MD, professor and chair of the Department of Hematology and Medical Oncology at the Emory University School of Medicine and chief medical officer at Emory’s Winship Cancer Institute, to discuss the FDA approval of the antibody-drug conjugate belantamab mafodotin (Blenrep), along with other BCMA-targeting agents for patients with multiple myeloma.

**Q:** What are the current strategies for targeting BCMA in multiple myeloma, and what advantages do they hold over conventional treatment?

**LONIAL:** There are, right now, 3 different ways to get to BCMA.

You can use the antibody-drug conjugate monomethyl auristatin F, you can do a bispecific, or what’s also known as a T-cell engager, or you can use chimeric antigen receptor (CAR) T-cell therapy.

The first approved drug to target BCMA, belantamab mafodotin, included patients with a median of 6 to 7 prior lines of therapy. For patients who do respond, the duration of response (DOR) is 11 months. I think that’s an important number to put in perspective because for every drug that has a 30% response rate, the median progression-free survival, or PFS, is about 3 months. No matter what drug you look at in that refractory myeloma setting, 30% equals 3 months. But the DOR [for belantamab mafodotin] really speaks to the tolerance of that treatment and the ability for responders to stay on treatment. That’s why I think it’s such an important step forward. The ocular toxicity is somewhat unique for myeloma drugs. It is more of an examination finding by an ophthalmologist or an optometrist; it does not always result in significant symptoms. And in fact, only 18% to 20% of the time it results in a change in visual acuity. I think the take-home message is that it is a really good option. It’s our go-to

option for triple-class refractory myeloma. Partnering with an eye care professional is part of the process, and it’s just something we should all get used to doing to figure out how to maximize the benefit from [belantamab mafodotin].

If you go to the T-cell engagers, I think this is a concept that we’ve seen with blinatumomab (Blinicyto) in acute lymphoblastic leukemia (ALL) and now lymphoma, where you’re basically targeting the tumor, and you’re targeting a T cell and bringing them in close proximity. I will tell you personally, I was skeptical that this approach would work in myeloma because I thought that T cells would be exhausted, and I wasn’t sure you’d be able to get them to work. But certainly, at the higher doses in the phase 1 trials for both teclistamab and the BMS (Bristol Myers Squibb) product, it appears that you’re getting responses over 65% to 70%. What we need to see is the durability of those responses, and what the mechanisms of failure are for this. Is it inducing ultimately T-cell exhaustion? Or are there new mechanisms of resistance that we just don’t know? But this is another way to go after BCMA.

The third is CAR T cells. CAR T cells I think everybody’s familiar with in terms of ALL and

diffuse large B-cell lymphoma. The only difference is BCMA is the target. What we see [with CAR T-cell therapy] is a very high overall response rate. And interestingly, the incidence of significant cytokine release syndrome or neurologic toxicity is much lower in BCMA-targeted CAR T cells than we've seen with CD19. We don't know if that's a function of BCMA or if it is a function of myeloma, but it seems like it's actually somewhat better tolerated overall. And at least from what we know that was presented by [Nikhil C.] Munshi, [MD,] the median progression-free survival is about 11 months as well. So, there are very active, very deep responses that last roughly 11 to 12 months on average.

I think the advantage that BCMA has over, for instance, CD38 or even SLAMF7, is that the target is expressed much more exclusively on plasma cells. So, the off-target impact is going to be less. And it gives us a second or third antibody target to go after that is really important. BCMA is a great target, its ligand is 1 of the reasons why myeloma cells become resistant. So, blocking BCMA, through any of these approaches, actually not only targets the tumor cell, but it also may help to overcome drug resistance. And those are really exciting opportunities.

**Q:** When it comes to belantamab mafodotin, what is the patient population that's best suited for this drug?

**LONIAL:** The FDA approval is for patients who are triple-class

refractory, so resistant to proteasome inhibitors, immunomodulatory agents, and anti-CD38 antibodies. For me, it would end up being a patient who's had 3 prior lines of therapy, and is still in a reasonable performance status to get any treatment at all.

**Q:** Can you talk a little more about the associated ocular toxicity?

**LONIAL:** Unfortunately, you can't treat the ocular toxicity per se. The best way to treat it is to hold the drug and let the toxicity [ease]. What I think is important and different from many other drugs, though, is that the half-life of belantamab mafodotin is long enough that, even if you have to hold a dose or 2 for 3 weeks, or oftentimes 6 weeks, most patients still maintain or improve their response. It's not like if you don't stay on schedule you're going to be in trouble. I think that's an important lesson we learned from the phase 2 DREAMM-2 study.

**Q:** What do you see as the next steps with belantamab mafodotin, or with any of the other BCMA-targeting therapies? Is it possible that they could move earlier in the treatment timeline?

**LONIAL:** I think the question is going to be, how do you partner them with other drugs? How does [belantamab mafodotin] fit in? And those trials are being done now, combining it with pomalidomide (Pomalyst), with bortezomib (Velcade), with lenalidomide (Revlimid). Then, another question coming up is, how do you sequence

those drugs? If a patient has been treated with one, can they respond to another? That's a question we've not been able to answer because most of the trials have excluded prior exposure to BCMA [therapy]. But now they're all including cohorts of prior BCMA therapy. I think we'll get an answer to that question in the next year.

**Q:** Is there any trial specifically in this area that you're looking forward to hearing about or that will really inform these issues?

**LONIAL:** What I'm most curious about with the T-cell engagers is longer follow-up to understand how long do these responses last? Because I think our hope with the CAR T cells was that perhaps the median duration of response might be longer than we've seen, but it's a one-and-done therapy. Once you're done with a CAR T-cell therapy you're not on any other therapies, which patients love. But with the T-cell engager giving a continuous therapy over time, maybe the response will last longer. We don't know the answer to that, and that's the big question we have to answer.

**Q:** What about multiple myeloma in the newly diagnosed setting? Where is the field headed when it comes to that group of patients?

**LONIAL:** I think in the newly diagnosed setting, we will likely move to quadruplet regimens. The question is going to be, how long do we continue treatment with all 4 drugs? At least at our center, we've adopted RVd

(lenalidomide, bortezomib, and dexamethasone) plus daratumumab (Darzalex), as a standard induction regimen for standard-risk patients. But we only give it for 4 cycles, collect stem cells, and take them to transplant, and then we go to risk adaptive maintenance afterward. I think the idea of continuing 4 drugs forever is not a very patient friendly approach, nor is it a very cost-effective approach. But the question is, can you use these drugs for short bursts of time to try to get where you want to get, and then come to something a little less intense on the back end?

**Q:** It seems like we're in a period of real innovation here in the multiple myeloma space. Would you agree with that? How would you characterize where the field is right now?

**LONIAL:** We have periods where a lot [of innovation] happens. The last time was probably 2016, when we had both elotuzumab (Empliciti) and daratumumab approved in the same 60-day period. We're seeing BCMA-targeted therapies come to the forefront of therapy and moving them into earlier lines of therapy, and figuring out how to do things like minimal residual disease (MRD)-driven therapy. If somebody is MRD-positive, is that where you treat with a BCMA-directed therapy early to try to eliminate that? I think those are exciting questions we're going to be able to answer.

Continued on page 503

# Case Study of Early-Stage Breast Cancer Treatment During the COVID-19 Pandemic

**A**s reported in a recent (2020) case study published in the *New England Journal of Medicine (NEJM)*, when a 62-year-old woman was found to have invasive ductal carcinoma, stage T2N0, physicians at Massachusetts General Hospital in Boston had to decide on a treatment plan that also took into account the demands of the coronavirus disease 2019 (COVID-19) pandemic.<sup>1</sup>

The patient had no known family history of breast or ovarian cancer when she discovered a lump in her left breast, from which a fibroadenoma had been excised 30 years earlier. This time, imaging revealed an irregular mass with spiculated margins that are a hallmark of malignancy. An ultrasound showed that the mass measured 3.1 cm by 1.5 cm by 1.2 cm, and the left axillary lymph nodes appeared normal. A biopsy was performed, and the cancer was determined to be hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative.<sup>1</sup>

*CancerNetwork*<sup>®</sup> also spoke with Anthony Lucci, MD, a breast surgical oncologist at The University of Texas MD Anderson Cancer Center in Houston, about how the standard approach toward the surgical management of patients with early-stage breast cancer, such as this one, had to rapidly evolve during the pandemic.

## Prepandemic Management of Breast Cancer

Before the COVID-19 pandemic, a patient with this profile would be counseled to consider up-front surgery, such as mastectomy or lumpectomy with radiation<sup>2</sup>—likely lumpectomy to preserve breast tissue and sensation.<sup>3,4</sup> A sentinel-node biopsy

would be performed to determine axillary involvement. Because this patient is of Ashkenazi Jewish descent, genetic counseling would be recommended to check for *BRCA1* or *BRCA2* mutations. Although the risks of lumpectomy—which include additional surgery if the tumor margins are positive, lymphedema, infection, seroma, and hematoma<sup>5,6</sup>—are no greater in women with *BRCA* mutations, their risk of contralateral breast cancer 20 years later is elevated by 26% to 40%.<sup>7</sup> This leads some to choose bilateral mastectomy.<sup>1</sup>

After surgery, the appropriate adjuvant therapy would be determined—typically, endocrine therapy, possibly with chemotherapy—depending on clinical features and test results, for a patient such as this one with HR-positive, HER2-negative breast cancer. Because this patient is past menopause, an aromatase inhibitor would be prescribed as a daily therapy for 5 to 10 years,<sup>8,9</sup> or the patient might be offered up-front tamoxifen followed by an aromatase inhibitor.<sup>10</sup>

For this patient, radiation would be a standard treatment after surgery. Radiation typically begins 4 to 8 weeks after surgery and is administered daily to the whole breast for 3 to 4 weeks. If chemotherapy is started after surgery, radiation may be postponed until after chemotherapy is finished to ensure maximum effectiveness of the chemotherapy treatment.<sup>11</sup>

## Recommendations on Multidisciplinary Care of Breast Cancer During COVID-19 Pandemic

Early in the pandemic, the Massachusetts Department of Public Health, in response

to the governor's state of emergency declaration, ordered all nonessential elective invasive procedures stopped to reduce staff and patient exposure to severe acute respiratory syndrome coronavirus 2 and preserve crucial equipment and staffing levels.<sup>1,12</sup> Massachusetts executed this order on March 18, 2020<sup>13</sup>; therefore, clinicians treating this patient had to consider an alternative treatment scenario. The patient's breast surgeon was part of a multidisciplinary clinic that included radiation oncology and medical oncology consultants, all of whom contributed to the revised plan of action.<sup>1</sup>

The clinic's team members relied on new guidelines issued by health care organizations such as the American Society of Breast Surgeons (ASBrS), which convened a COVID-19 Breast Cancer Consortium to outline recommendations on multidisciplinary care of breast cancer during this time.<sup>14</sup> Chief among the Massachusetts General team's concerns was preventing tumor growth should surgery be delayed in this patient, as well as the design of an appropriate medication regimen in the absence of surgery. The team also needed to consider whether radiation could be safely postponed or, if not, whether the duration of radiation treatment could be shortened by implementing hypofractionated or accelerated regimens.<sup>1</sup>

## Neoadjuvant Endocrine Therapy

The new ASBrS guidelines state that, as an alternative to up-front surgery, many patients with early-stage breast cancer can be given neoadjuvant endocrine therapy.<sup>14</sup> Massachusetts General issued its own guidelines for breast cancer surgeons,

including the fact that patients with estrogen receptor (ER)-positive tumors may delay surgery for as long as 6 to 12 months if neoadjuvant endocrine therapy is taken during that time.<sup>15</sup>

Massachusetts was far from the only state to impose restrictions on surgeries at the start of the pandemic. “[I]n [Texas]... we were not supposed to perform what were considered elective or low-risk operations on patients with low-risk cancers,” said Lucci. “That is, I think, the biggest difference between before and after the pandemic—the timing of the operation.”

To determine whether a patient truly has a low-risk cancer that can be treated with alternatives to surgery, the ASBrS Consortium recommends that clinicians separate patients with newly diagnosed breast cancer into high-intermediate, and low-priority treatment categories.<sup>14,16</sup> This judgment is based on the diagnosis itself, how quickly the disease is advancing, and any complicating factors. Also taken into account are overall patient health, COVID-19 risk in the region, and adequate hospital resources (eg, availability of operating rooms, staff, personal protective equipment, and good sanitation and ventilation).<sup>14,17</sup> The patient in the *NEJM* case study, who is postmenopausal with early-stage, HR-positive cancer, would fall into the intermediate-priority category; the decision to delay surgery may be appropriate, which, according to Lucci, is not uncommon.

“I can tell you that during the pandemic we actually had many patients with this exact same scenario, and this was actually quite frequent,” Lucci said. “One of the things it does is, it engenders a lot of anxiety for the patients, which is absolutely understandable because they now have this tumor and they are not sure if it is going to grow, if it is going to progress. During this time, [they] cannot get to the operating room, and that is a real true concern.”

Patients in this situation now are likely to begin neoadjuvant endocrine therapy, the goal of which, according to Lucci, is to “shrink the tumor to allow breast-conserving therapy.” According to



### Expert Interview With Anthony Lucci, MD

Lucci discusses the rapid evolution of clinical management in patients with early-stage breast cancer during the COVID-19 pandemic.



To see the full video with Lucci, scan the code.

the *NEJM* report, aromatase inhibitors are superior to tamoxifen when it comes to neoadjuvant endocrine therapy<sup>1</sup>; the results of 1 study indicated that 69.8% of postmenopausal patients taking aromatase inhibitors for 3 months had a partial or complete response, potentially raising the potential for negative surgical margins and a more satisfactory breast appearance after surgery.<sup>18</sup> The report also asserts that disease progression is unlikely during neoadjuvant endocrine therapy.

However, during the standard 3- to 6-month (or even longer) course of neoadjuvant endocrine therapy, there is always the possibility of the disease progressing.<sup>19</sup> Patients who opt to skip or delay surgery or chemotherapy in favor of neoadjuvant endocrine therapy should adhere to a firm follow-up schedule, including imaging if necessary. It is suggested that patients see their clinicians 4 to 6 weeks after beginning neoadjuvant endocrine therapy and at regular intervals for about 3 months. If at this time the tumor has grown, surgery or chemotherapy should be immediately considered.<sup>14</sup>

Lucci and his team found that the central question they had to keep asking when considering how to proceed after diagnosis was whether a patient was truly low risk and could be treated with alternatives to surgery or chemotherapy. “[What we did was] to try to identify patients who have favorable biology and a low risk of progression so they could be placed on endocrine therapy,” he said.

A benefit of postponing surgery is that it allows for genetic testing results that

can shed additional light on treatment decisions, such as whether to proceed with chemotherapy.<sup>1</sup> Because the patient in the *NEJM* case study had clinical characteristics that conflicted in terms of whether chemotherapy would be helpful (ie, a large tumor, but one that is strongly HR positive), her clinicians may want to rely on a genomic testing assay, such as the 21-gene Oncotype Dx Breast Recurrence Score test, for assistance in making a decision. This test allows a more nuanced examination of factors that will determine whether surgery and/or chemotherapy are warranted.

### Oncotype DX Assay Helps Guide Treatment

The Oncotype Dx Breast Recurrence Score test enables providers to obtain a more precise assessment of the risk of cancer recurrence and gauge the necessity of chemotherapy. This assay uses small amounts of tumor, harvested during a core-needle biopsy, to analyze the RNA expression of 21 distinct genes. The data are then synthesized, generating a recurrence score from 0 to 100. Patients who have high clinical risk but a low recurrence score (<11) on the Oncotype Dx test may opt to rely on endocrine therapy alone, whereas patients who have low clinical risk but a high recurrence score ( $\geq 31$  or  $\geq 26$ , depending on the specific trial) are likely to benefit from chemotherapy.<sup>20</sup>

Many patients who received new diagnoses MD Anderson this past spring ended up being told that traditional treatments such as surgery and chemotherapy would be postponed due to the pandemic, according to Lucci. But being able to as-



sign recurrence scores to patients using the Oncotype Dx Breast Recurrence Score test was a game changer. “No one wants to wait to get this cancer removed,” he said. “But then...we could tell them it was OK: ‘We have a plan. We can test your tumor. If it has favorable biology, the likelihood of you progressing on endocrine therapy will be exceedingly small.’ I do think in the future we’ll be able to use this tool much more to guide our neoadjuvant therapies.”

### The TAILORx and Other Studies

As chemotherapy may be especially risky during the COVID-19 pandemic, it is prudent to avoid it if possible. But does opting out of chemotherapy raise the chances of poorer outcomes? The large Trial Assigning Individualized Options for Treatment (TAILORx) study (NCT00310180), which followed more than 10,000 women with HR-positive, HER2-negative, axillary node-negative breast cancer over a 9-year period, provides some clarity. In this trial, patients were given postsurgery treatment based on their recurrence scores on the Oncotype DX assay. Women with low recurrence scores were administered endocrine therapy only, and women with high recurrence scores had chemoendocrine therapy. Those whose scores were in the intermediate range were randomized to either type of therapy.<sup>21</sup>

The patient cohort taking endocrine therapy had an overall 5-year survival rate of 98%, providing further evidence that skipping chemotherapy is an appropriate choice for low-risk patients. Women who were randomized to either endocrine therapy or chemoendocrine therapy had similar outcomes, with 5-year overall survival rates of 93.9% and 93.8%, respectively; those 50 years or younger in this group received a small benefit from chemotherapy.<sup>21,22</sup>

According to a National Academy of Medicine article on this study, “The TAILORx trial demonstrated that approximately 70% of women with HR-positive, HER2-negative, node-negative breast cancer can safely avoid chemotherapy, including all women with [recurrence score] RS

of 0 to 15 and women above age 50 with RS of 0 to 25.”<sup>23</sup>

“The TAILORx study...has changed significant[ly]...how we treat patients,” Lucci said. “This is a practice-changing study. We now know that patients over [age] 50 with a score of 0 to 25 have no inferior outcome by removing chemotherapy. We now know we can safely avoid the kind[s] of [adverse] effects and morbidities associated with chemotherapy in these patients with scores in that 0-to-25 range.”

In the translational study of the New Primary Endocrine-therapy Origination (TransNEOS) study, 295 postmenopausal women under age 75 received 24 to 28 weeks of neoadjuvant therapy with the aromatase inhibitor letrozole and submitted samples for the Oncotype Dx Breast Recurrence Scores test. Women whose recurrence scores were below 31 had a very low incidence of disease progression. Fewer than 1% of women whose scores were below 18 experienced disease progression, and 4% of those whose scores fell between 18 and 30 saw their disease progress. However, 17% of patients whose scores were 31 or higher had disease progression. The much greater likelihood of disease progression in patients with higher recurrence scores necessitates a conversation about whether these patients should have surgery or neoadjuvant chemotherapy.<sup>24</sup>

However, another study, the SAFIA trial, enrolled 308 pre- and postmenopausal patients with stages II and III luminal A/B HER2-negative breast cancer. Out of the 308 patients, 70 were excluded for having recurrence scores of 31 or higher. The remaining 238 patients received neoadjuvant endocrine therapy for 4 months and were measured for disease response. The study found no significant correlation between recurrence score and response to neoadjuvant endocrine therapy.<sup>25</sup>

### Patient Outcomes Pre- and Postmenopause

The multidisciplinary clinic team in the *NEJM* report determined that they could not proceed with surgery on the patient because of COVID-19 restraints. They opted

for neoadjuvant endocrine therapy with an aromatase inhibitor and scheduled a 2-month follow-up.<sup>1</sup>

The decision made by the clinic team may have been different had the patient been younger. Less clinical data exist on the use of neoadjuvant endocrine therapy in premenopausal women than on postmenopausal women. Although results from the GEICAM/2006-03 study (NCT00432172) demonstrated that neoadjuvant chemotherapy offers better results than neoadjuvant endocrine therapy in premenopausal patients, neoadjuvant endocrine therapy still deserves consideration among this cohort of women as a first-line treatment during the pandemic.<sup>8,26,27</sup> Chemotherapy is typically favored for women 50 years or younger; however, the risks of becoming immunosuppressed as a result of chemotherapy and being more vulnerable to infection must be taken into account.<sup>21,28</sup>

One study examined data on 76 women with stages I through III ER-positive, HER2-negative breast cancer who were part of the Young Women’s Breast Cancer Study. All were 40 years or younger at the time of diagnosis, had tumor specimens evaluated with the 21-gene assay test, and had undergone neoadjuvant chemotherapy. The study’s authors found that patients who had a higher recurrence score had a greater benefit from chemotherapy in the form of no residual invasive tumor. Patients whose recurrence scores were lower exhibited less of a response to chemotherapy and were less likely to have no residual invasive tumor.

In these circumstances, chemotherapy may very well be overkill, exposing the patient to more risk than benefit; alternative treatments such as endocrine therapy deserve greater consideration in such cases.<sup>29</sup>

### Moving Forward

Lucci emphasized that the information provided by the Oncotype Dx Breast Recurrence Score test will prove valuable should standard breast-cancer treatment plans be derailed for any reason. “We have been able to resume doing all of our cancer operations, and we’re not having to triage patients currently, but we do not know that

there could not be additional [COVID-19] spikes,” he said. “[I]n the future this could become a vital tool to really stratify and guide patients to the right therapy.”

It is also worth keeping in mind that treatment of breast cancer is about not only medications and surgeries but also providing clear information and helping to allay anxieties. The virtual nature of some visits may add to the challenge of keeping patients apprised of all developments. It is important to ask the patient how they are doing emotionally, acknowledge their fears about possible delays in treatment, and reassure them that all treatment approaches have been considered with the best outcomes in mind.<sup>1</sup> ■

Medical writing support provided by Laurie Saloman, MS.

## REFERENCES

- Spring LM, Gupta A, Reynolds KL, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(11):1477-1486. doi:10.1001/jamaoncol.2016.1897
- Fisher B, Jeong J-H, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347(8):567-575. doi:10.1056/NEJMoa020128
- Wellisch DK, DiMatteo R, Silverstein M, et al. Psychosocial outcomes of breast cancer therapies: lumpectomy versus mastectomy. *Psychosomatics*. 1989;30(4):365-373. doi:10.1016/S0033-3182(89)72241-6
- Pozo C, Carver CS, Noriega V, et al. Effects of mastectomy versus lumpectomy on emotional adjustment to breast cancer: a prospective study of the first year postsurgery. *J Clin Oncol*. 1992;10(8):1292-1298. doi:10.1200/JCO.1992.10.8.1292
- Coopey S, Smith BL, Hanson S, et al. The safety of multiple re-excisions after lumpectomy for breast cancer. *Ann Surg Oncol*. 2011;18(13):3797-3801. doi:10.1245/s10434-011-1802-4
- Shah C, Arthur D, Riutta J, Whitworth P, Vicini FA. Breast-cancer related lymphedema: a review of procedure-specific incidence rates, clinical assessment AIDS, treatment paradigms, and risk reduction. *Breast J*. 2012;18(4):357-361. doi:10.1111/j.1524-4741.2012.01252.x
- Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112
- Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2020;18(4):452-478. doi:10.6004/jnccn.2020.0016
- Pan H, Gray R, Braybrooke J, et al; Early Breast Cancer Trialists' Collaborative Group. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830
- Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352. doi:10.1016/S0140-6736(15)61074-1
- Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. *J Clin Oncol*. 2005;23(9):1934-1940. doi:10.1200/JCO.2005.04.032
- Factsheet: state action related to delay and resumption of “elective” procedures during COVID-19 pandemic. American Medical Association. Accessed October 12, 2020. <https://www.ama-assn.org/system/files/2020-06/state-elective-procedure-chart.pdf>
- Order of the Commissioner of Public Health. Massachusetts. March 15, 2020. Accessed October 12, 2020. <https://www.mass.gov/doc/march-15-2020-elective-procedures-order/download>
- COVID-19 pandemic Breast Cancer Consortium's considerations for re-entry. American Society of Breast Surgeons. Accessed October 12, 2020. <https://www.breastsurgeons.org/docs/covid19/reentry.pdf?v1>
- Re-entry tool for breast surgeons. Massachusetts General Hospital. May 6, 2020. Accessed October 12, 2020. <https://www.massgeneral.org/surgical-oncology/about/news-and-events/re-entry-tool-for-breast-surgeons>
- Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. The COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat*. 2020;181(3):487-497. doi:10.1007/s10549-020-05644-z
- Prachand VN, Milner R, Angelos P, et al. Medically necessary, time-sensitive procedures: scoring system to ethically and efficiently manage resource scarcity and provider risk during the COVID-19 pandemic. *J Am Coll Surg*. 2020;231(2):281-288. doi:10.1016/j.jamcollsurg.2020.04.011
- Dixon JM, Renshaw L, Macaskill EJ, et al. Increase in response rate by prolonged treatment with neoadjuvant letrozole. *Breast Cancer Res Treat*. 2009;113(1):145-151. doi:10.1007/s10549-008-9915-6
- Allevi G, Strina C, Andreis D, et al. Increased pathological complete response rate after a long-term neoadjuvant letrozole treatment in postmenopausal oestrogen and/or progesterone receptor-positive breast cancer. *Br J Cancer*. 2013;108(8):1587-1592. doi:10.1038/bjc.2013.151
- Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817-2826. doi:10.1056/NEJMoa041588
- Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med*. 2018;379(2):111-121. doi:10.1056/NEJMoa1804710
- Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373(21):2005-2014. doi:10.1056/NEJMoa1510764
- Makower D, Sparano JA. Breast cancer management in the TAILORx era: less is more. December 17, 2018. Accessed October 12, 2020. <https://nam.edu/breast-cancer-management-in-the-tailorx-era-less-is-more/>
- Iwata H, Masuda N, Yamamoto Y, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, Her2-negative breast cancer: the TransNEOS study. *Breast Cancer Res Treat*. 2019;173(1):123-133. doi:10.1007/s10549-018-4964-7
- Al-Saleh KA, Bounedjar A, Oukkal M, et al. Prediction of response to neoadjuvant hormonal therapy (NAH) using upfront oncotype Dx recurrence score (RS): results from the SAFIA phase III trial. *J Clin Oncol*. 2020;38(suppl 15):594. doi:10.1200/JCO.2020.38.15\_suppl.594
- Spring LM, Specht MC, Jimenez RB, et al. Case 22-2020: a 62-year-old woman with early breast cancer during the COVID-19 pandemic. *N Engl J Med*. 2020;383(3):262-272. doi:10.1056/NEJMcpc2002422
- Alba E, Calvo L, Albanell J, et al; GEICAM. Chemotherapy (CT) and hormonal therapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. *Ann Oncol*. 2012;23(12):3069-3074. doi:10.1093/annonc/mds132
- Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and economic risk to guide the use of adjuvant therapy for breast cancer. *N Engl J Med*. 2019;380(25):2395-2405. doi:10.1056/NEJMoa1904819
- Sella T, Gelber SI, Poorvu PD, et al. Response to neoadjuvant chemotherapy and the 21-gene breast recurrence score in young women with estrogen receptor-positive early breast cancer. *J Clin Oncol*. 2012;30(15):514. doi:10.1200/JCO.2020.38.15\_suppl.514

# Supporting Decision-Making on Fertility Preservation Among Adolescent and Young Adult Women With Cancer

Jackelyn B. Payne, MPH, MA<sup>1</sup>; Christopher R. Flowers, MD, MS<sup>2</sup>; Pamela B. Allen, MD<sup>3</sup>

<sup>1</sup>Department of Psychology, Stony Brook University, Stony Brook, New York; <sup>2</sup>Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Houston, Texas; <sup>3</sup>Department of Hematology and Medical Oncology, Emory University Winship Cancer Institute, Atlanta, Georgia

**ABSTRACT:** Adolescents and young adults (AYAs) with cancer constitute approximately 70,000 patients diagnosed each year. Survival rates for AYAs with cancer have increased steadily in recent decades due to improvements in therapeutic regimens and early detection. Given the large and growing number of AYA cancer survivors, additional research is needed on the immediate and long-term psychosocial support required for this population including family planning and fertility. Fertility and fertility preservation in female AYAs, in particular, is historically understudied and has psychologically relevant ramifications distinct from male AYAs. Decision science can contribute to this area of oncological care and has implications for clinical encounters and research concerning female AYA patients with cancer. Patient-centered care and shared decision-making that integrates recent research regarding fertility preservation in the context of cancer treatment can improve outcomes for AYA cancer survivors.

## PERSPECTIVE

**Elizabeth S. Constance, MD**  
discusses fertility preservation  
during gonadotoxic therapy on  
page 500

## Introduction

Adolescents and young adults (AYAs) with cancer constitute approximately 70,000 patients diagnosed each year,<sup>1</sup> accounting for about 5% of cancer diagnoses.<sup>2</sup> AYAs are classified as patients diagnosed between the ages of 15 and 39 and are biologically<sup>3</sup> and psychosocially<sup>4</sup> distinct from younger and older age

groups. Survival rates for AYAs with cancer have increased steadily in recent decades, primarily due to improved therapeutic regimens.<sup>5</sup> Currently, AYAs across all cancers have a 5-year survival rate of approximately 80%.<sup>6</sup> Given the number of AYA cancer survivors, researchers have begun to study the psychosocial needs of this growing population, including dis-

ruption of education and career development, employment, substance abuse, family planning, and fertility.<sup>7</sup>

Cancer treatments are detrimental to reproductive functioning including fertility. However, fertility in female AYAs is historically understudied and has psychologically relevant ramifications distinct from male AYAs.<sup>8</sup> Until recently, there were few fertility preservation options available for women. Although they are becoming more common, fertility preservation procedures for women are more invasive, more expensive, and delay cancer treatment much longer than fertility preservation procedures for men.<sup>9,10</sup> In addition, many providers do not prioritize and are hesitant to discuss fertility preservation with female AYA patients.<sup>11</sup> Uncertain risks and lack of information about future fertility, coupled with little time to make a potentially life-changing

decision about pursuing fertility preservation before beginning cancer treatment, creates a complex clinical and psychosocial decision-making scenario for AYA women diagnosed with cancer.<sup>12</sup>

Decision science, in the context of medical treatment decision-making, is understudied in oncological care. As medical researchers continue to improve survival rates and fertility options for this population of patients with cancer, the psychological study of treatment decision-making in the context of fertility is needed. This review aims to summarize the work in this area to date and to define future areas for scientific inquiry.

## Oncofertility

Oncofertility is the study of fertility preservation in the context of cancer diagnosis, treatment, and survival.<sup>11,13</sup> In women, an individual's ovarian reserve, or number of oocytes, decreases over time. For fertility and normal endocrine function to be maintained, the menstrual cycle routinely develops oocytes from the ovarian reserve, secreting essential hormones in the process. Disturbance of the ovarian reserve, especially in younger women, has immediate and long-term effects on health and fertility.<sup>13</sup>

For AYA women, the cancers with the highest incidence rates are breast cancer, thyroid cancer, and lymphoma.<sup>14</sup> **(Table 1)** A growing body of research studies suggests that AYAs have biological and genetic differences from pediatric and older adult patients with cancer.<sup>2</sup> For example, AYA breast patients with cancer are more likely to present with genetic mutations, making the cancer more aggressive and harder to treat than in older adult patients. Triple-negative breast cancer is overrepresented in the AYA patient population. Thyroid cancer and lymphomas in AYAs are also more likely to exhibit mutational characteristics than in older adult patients. Due to this, and to their relative health compared with older adults, AYA patients with cancer are more likely to receive aggressive therapy regimens.<sup>14</sup>

**TABLE 1. Age-Adjusted Rate of Cancer Incidence for Common AYA Cancers in Women by Age Group**

Cancer type	15-19	20-24	25-29	30-34	35-39
Brain and other nervous system	2.1	1.9	2.6	3.0	3.2
Breast	0.2	1.6	10.2	29.6	61.3
Cervix	~	0.7	4.6	11.1	13.7
Colon and rectum	1.3	2.4	3.6	6.2	11.0
Hodgkin lymphoma	3.4	4.4	3.9	3.4	2.4
Leukemias	2.3	2.2	2.7	3.4	4.2
Melanomas of the skin	0.9	3.5	7.9	12.8	15.6
Non-Hodgkin lymphoma	1.3	2.1	2.6	3.7	5.4
Thyroid	5.1	10.4	17.0	24.6	30.3

Rates are the number of cases (or deaths) per 100,000 people and are age-adjusted to the 2000 US standard population. Rates are based on 2017 US cancer registry data.

~ Rates are suppressed if fewer than 16 cases were reported in a specific site.

Source: US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2020.

The common treatments for AYA cancer, chemotherapy and radiation, often result in significantly impaired fertility in women and men.<sup>15</sup> **(Table 2)** (A notable exception is the frontline therapy for Hodgkin lymphoma, the ABVD [doxorubicin, bleomycin, vinblastine, dacarbazine] regimen.<sup>16</sup> In addition, there are non-reproductive health issues that may result in the long term due to dysregulation of the endocrine system, including the cardiovascular system and bone health.<sup>13</sup> The mechanisms for this are still being studied, as better treatments are relatively new. Although dependent on the type and duration of treatment cycles, chemotherapy regimens designed to destroy cancer cells also are damaging to ovarian reserves. Regarding radiation, exposure to even small amounts lead to premature ovarian failure.<sup>13</sup>

## Fertility Preservation

Advances in fertility preservation methods have created options for young women that were previously unavailable. With the emerging interest in these methods and concerns about the associated psychological ramifications, expert guidance

on the effectiveness and best practices for implementation in clinics were needed. The International Network on Cancer, Infertility, and Pregnancy (INCIP) and the European Society of Gynecological Oncology (ESGO) are currently tasked with creating recommendations for the presentation of fertility preservation options and standards of care for AYA cancer patients.<sup>15</sup> Currently, the options available to women who are able and willing to preserve fertility before treatment are oocyte or embryo cryopreservation (slow freezing of tissue), ovarian transposition (relocation of ovaries within the body), or administration of follicle-protecting agents.<sup>17</sup> Several experimental options are also emerging, including the use of artificial ovaries and in vitro follicle cultures, which are currently being studied in nonhuman primates.<sup>15</sup> Each method comes with advantages and disadvantages, which are outside the scope of this review.

## Psychological Factors

The potential side effects and risk of failure of fertility preservation efforts,



**TABLE 2. Impact of Common Cancer Treatments on Fertility in AYA Women**

Treatment	Impact	Relevant AYA cancer type
<b>Bone marrow or stem cell transplant</b>	High doses of chemotherapy and/or radiation prior usually permanently damage ovaries	Leukemias, lymphomas
<b>Chemotherapy</b>	Kills oocytes; dependent on combination of drugs and dosage	Many cancer types
<b>Hormone therapy</b>	May affect hormones that affect ovulation	Breast
<b>Radiation therapy</b>	Radiation aimed at or around reproductive organs may affect functioning; high doses destroy eggs in the ovary; may cause scarring of the uterus; may disrupt hormones that affect ovulation	Brain & other nervous system, cervix, colon and rectum
<b>Surgery</b>	Tumors in or near the reproductive organs may be removed; may cause scarring which affects functioning	Cervix, colon and rectum
<b>Targeted therapy and immunotherapy</b>	Certain drugs may cause ovarian failure; little is known about the effect on fertility	Many cancer types

Source: American Cancer Society, 2020.

coupled with potential uncertainty about future family plans, often makes the decision about whether to pursue pretreatment preservation difficult.<sup>12</sup> (Table 3<sup>9,12,18-22</sup>) Pursuing fertility preservation also delays cancer treatment,<sup>9</sup> contributing to the pressure and uncertainty already present in the decision-making process. In addition, the expense and time needed to pursue these methods serve as barriers to choosing this option at all. The stress of dealing with an unexpected cancer diagnosis, and urgency to begin treatment for more aggressive cases, may also lessen the attention young women and their families give to fertility preservation before beginning treatment.<sup>12</sup>

Historically, AYAs were not treated as a distinct patient population. Oncologists treating children and teenagers were trained in pediatric oncology, but at the age of 18 patients became adults and were treated similarly to all older adults. As the psychosocial needs of young adults gained more attention, the AYA subgroup became clinically distinct.<sup>4</sup> Still, fragmen-

tation of care and lack of standard protocols prevent many AYA patients with cancer and survivors from receiving the specialized care most relevant to them, including fertility planning.<sup>4,7</sup> Developmentally, AYAs have distinct needs from children and older adults. The adult brain is not fully formed until around the age of 30, and the effects of cancer treatment on AYA development are understudied.<sup>14</sup> AYAs also are in a phase of their life where they may not have developed the coping skills to deal with traumatic disruptions to life goals such as a cancer diagnosis. In addition, considering the stress of a potential lack of education attainment, financial instability, and the side effects of treatment, AYA cancer survivors report difficulty in creating and maintaining meaningful sources of social support.<sup>23</sup>

Given the stressful context of cancer diagnosis, treatment, and survivorship specific to AYA patients with cancer, making a decision about family planning before treatment is a difficult stressor to

cope with among many other difficult stressors. Additionally, it is important to recognize individual differences in coping with the potential loss of fertility due to cancer treatment.

### Decision-Making and Oncology

For AYA patients with cancer, fertility is the second most important factor when choosing a treatment, surpassed only by survival.<sup>13</sup> Decision science incorporates several fields and methodologies that examine how individuals make decisions. In health care, medical decision-making research frequently utilizes psychological inquiry into individual values, interpersonal dynamics, and structural barriers affecting decisions about prevention and treatment of health conditions.<sup>24</sup>

### Patient-Centered Care and Shared Decision-Making

Over the past few decades, patient-centered care has grown from a new buzzword in health care to a paradigm with a growing bed of evidence and funding. Patient-centered care refers to a way of delivering medical care that encourages active collaboration between patients, their families and caregivers, and providers.<sup>25</sup> The incorporation of patient-centered care shifts the aim of medical practitioners from acting upon a patient to acting *with* a patient. In this model of care, the patient is meant to be viewed as a consumer with values and preferences.<sup>26</sup>

Shared decision-making is a core value of patient-centered care. It is an iterative process of communication between a provider or care team and a patient about treatment options and risks, as well as the patient's personal preferences and values. When implemented, shared decision-making between patients and providers reduces decisional conflict, feelings of being uninformed, depersonalization of the individual, passivity, and indecision - all of which are detrimental to well-being and satisfaction.<sup>27,28</sup>

Patients may also bring additional chal-

lenges to their treatment decision-making, including cognitive factors, such as limited knowledge of treatment options, insufficient numeracy, and health literacy to understand risk and probability of various outcomes;<sup>29,30</sup> and emotional factors, such as decisional conflict and uncertainty.<sup>24</sup> As shared decision-making becomes more prevalent in cancer treatment decision-making, addressing the barriers to informed decision-making in clinical populations emerges as an essential factor for improving patient-centered outcomes.<sup>31,32</sup>

Concepts such as decisional conflict, decisional regret, and values clarification are engrained in the shared decision-making literature<sup>28</sup> and apply to the dilemma female AYA patients with cancer face regarding fertility preservation. In one qualitative study, values clarification exercises administered to adolescent girls facing fertility loss indicated that all of the participants strongly desired the ability to conceive children in the future, although participants had different coping styles for dealing with the loss of this ability.<sup>8</sup> The psychological understanding of the mechanisms of decision-making is also relevant to cancer decision-making specifically, illuminating the need for understanding the cognitive and emotional factors relevant to the components of informed, shared decision-making.<sup>24</sup>

### Oncofertility and Decision-Making

A recent review<sup>12</sup> of factors that make fertility preservation decisions difficult for women found several internal and external factors at play. Externally, lack of information, improper timing of information, and poor patient-provider communication prevent women from making informed decisions. In addition, uncertainty about negative outcomes of fertility preservation procedures makes decision-making difficult, including the effect of needing to delay cancer treatment to perform the procedure and potential complications that could arise

**TABLE 3. Factors Complicating Decision-Making Regarding Fertility Preservation in AYA Women With Cancer**

Control	Factor
<b>External factors</b>	Information provision <ul style="list-style-type: none"> <li>▪ Lack of or incomplete information about risk or options<sup>a</sup></li> <li>▪ Timing of discussion<sup>12,18,19</sup></li> <li>▪ Patient-provider communication<sup>19</sup></li> </ul>
	Referral from oncology to fertility consultation <ul style="list-style-type: none"> <li>▪ Physician recommendation<sup>12,20</sup></li> <li>▪ Provider's prioritization of fertility<sup>12</sup></li> </ul>
<b>Internal factors</b>	Organizational and communication issues between care teams <sup>a</sup>
	Financial barriers <ul style="list-style-type: none"> <li>▪ Cost of treatment<sup>12,20,21</sup></li> </ul>
<b>Internal factors</b>	Perceived risks <ul style="list-style-type: none"> <li>▪ Delaying cancer treatment<sup>8,12,20</sup></li> <li>▪ Aggravating hormonal cancer<sup>12</sup></li> <li>▪ Consequences of a future pregnancy on health of the child or mother<sup>21</sup></li> </ul>
	Life circumstances <ul style="list-style-type: none"> <li>▪ Parity prior to diagnosis<sup>12,22</sup></li> <li>▪ Relationship status<sup>12,21</sup></li> <li>▪ Difficulty conceiving prior to diagnosis<sup>21</sup></li> </ul>

with post treatment pregnancy. For women with cancers of the reproductive system, the risks of aggravating a malignancy with further reproductive system procedures are also a factor to take into consideration. Fragmentation of care at the organizational level prevents many women from having the full attention of a provider advocate to help make sense of the factors important to this decision, and as a result, some women may choose not to pursue fertility preservation and complicate an already complex provider care team. The researchers also found that for providers not specialized in AYA psychosocial issues, fertility preservation is not a priority and may be conveyed as such in the presentation of treatment options for AYA women. Based on these findings, there exists a clear need for organizational- and interpersonal-level intervention at the point of fertility preservation decision-making. Thorough, clear presentation of the options available to women and associated risks is essential.

Internally, there are key factors women must address when making this decision.<sup>12</sup> When faced with an unexpected

cancer diagnosis, AYAs are faced with significant decisions with implications for their futures, and these decisions must usually be made quickly. For many, family planning is not something they may have expected to think about for several years. In this situation, it is not uncommon for women to enter what the review describes as “survival mode,” or the immediate prioritization of survival. As a result, the impact on fertility may not be at the forefront of a treatment decision. Reinforced by oncologists concerned about disease progression, AYAs tend to opt for the more aggressive regimens that ensure the highest chance of survival. In addition to this dilemma, women must weigh the costs and benefits of financially committing to such a procedure, as well as reckon with the potential impact on their personal lives and relationship dynamics.<sup>33</sup>

### Implications for Clinical Settings

Multidisciplinary programs that target the physical and psychosocial needs of AYA patients with cancer hold promise for significantly improving the quality

**TABLE 4. Strategies to Improve Decision-Making Regarding Fertility Preservation in AYA Women With Cancer**

Factor	Strategy
<b>External factors</b>	
<b>Information provision</b>	Providers should be prepared to discuss fertility preservation with all AYA female patients and discussions should occur as early as possible. Discussions should be documented in the medical record <sup>18,36</sup>
<b>Referral from oncology</b>	Providers should default to referring all AYA female patients to a fertility specialist <sup>36</sup>
<b>Financial barriers</b>	Policy-level change in access to health care and insurance coverage
<b>Internal factors</b>	
<b>Perceived risks</b>	Accurately and thoroughly communicating the known risks of fertility loss associated with treatment options Communication of research findings from providers Development and implementation of decision aids to guide patients in thinking through risks and options <sup>37</sup>
<b>Decisional conflict</b>	Development and implementation of decision aids to guide patients in thinking through risks and options <sup>37</sup>
<b>Life circumstances</b>	Ensuring providers discuss fertility preservation with all patients, regardless of assumptions or biases about the patient's personal situation <sup>20</sup>

of life of patients and may help patients emotionally cope with cancer. One such program increased fertility preservation referrals and procedures by designating a multidisciplinary program to provide education about fertility preservation to eligible patients.<sup>34</sup> A recent systematic review also found that women who receive targeted fertility preservation counseling exhibit improved coping over time, and reduced regret and dissatisfaction with care long-term.<sup>35</sup> Guidelines for how to discuss fertility preservation with AYA patients with cancer are a recent development, and little research has yet to be done on the long-term effects of implementing satisfactory interventions to improve decision-making. Within the context of shared decision-making, fertility preservation conversations should be incorporated into the emerging paradigm for patient-centered decisions about treatment (Table 4).

Another method for addressing these

barriers to informed decision-making is the use of evidence-based decision aids, which can be videos, written information, or a product in another electronic format providing information about options, and may include coaching from a provider. Sometimes, these include values-clarification exercises, as well as information about potential priorities of care one should consider when making a treatment decision, including financial toxicity, logistics and timelines of treatment options, etc.

Decision aids are effective at improving patient involvement in medical decision-making and enabling them to be more knowledgeable and confident in their decisions. They may also improve outcomes such as quality of life and adherence to the chosen treatment.<sup>38,39</sup> A recent systematic review of decision aids specifically designed to support fertility preservation decision-making found that their use decreased decisional conflict

and increased knowledge about fertility planning, and users reported high overall satisfaction with them. However, only 2 such aids are currently available to AYA patients with cancer, and they are not tailored specifically to women.<sup>37</sup> Building on the success of these aids, future work should develop and tailor them to improve psychosocial outcomes for female AYA cancer survivors.

### **Unmet Needs of AYA Women Considering Fertility Preservation**

The decision about whether to pursue fertility preservation is complicated for AYA women diagnosed with cancer. Despite tremendous strides made in recent years to not only define oncofertility as a field of study,<sup>11</sup> but also to determine factors that make fertility preservation decisions difficult, little is known about the actual risk of fertility loss for AYA women with cancer. Current clinical guidelines are often based on data from pediatric cancer survivors due to the lack of longitudinal and epidemiological studies with diverse samples of this relatively new age group.<sup>40</sup> These studies take time and are expensive to conduct, but have tremendous implications for fertility loss in AYA cancer survivors. Fertility loss due to cancer treatment depends on a number of factors in addition to the type of cancer and treatment, including individual differences in hormone levels before the cancer diagnosis and the variety of combinations of treatments and comorbidities in patients. The risk of fertility loss is currently difficult to predict, which in turn makes patient-provider communication and shared decision-making more difficult. Data indicating the risk of fertility loss by cancer type, treatment type, and other factors are necessary to determining treatment guidelines. In addition, as research progresses on fertility preservation options and improves outcomes, long-term health and psychosocial effects of undergoing, or not undergoing, fertility preservation treatment will be needed.

Additional unmet needs of AYA cancer survivors include high financial burden, negative impact on achievement regarding education and work, impaired relationships, and uncertainty about family planning, sexual functioning, and struggles with physical and mental health.<sup>21,33,41</sup> Anxiety, self-blame, anger, and stress due to fertility loss also contribute to the difficulties experienced by this specific group. AYA women cancer survivors, in particular, suffer from negative psychosocial effects of cancer, including changes in physical appearance and functioning, emotional coping, and changes in social roles and in relationships, which exacerbate the already difficult psychological ramifications of fertility loss.<sup>42</sup> Although the long-term impact of informed, shared decision-making on these outcomes has yet to be fully explored in AYA women cancer survivors, the psychological study of decision-making provides several opportunities for further inquiry into this area of research. This includes best practices for shared decision-making between patients and providers, coping styles and strategies, sense of control and self-efficacy in decision-making, values clarification, and decisional conflict and regret.<sup>8,43</sup> Decision aids are an empirically validated way of incorporating shared decision-making. Currently, there are only 2 peer-reviewed decision aids regarding fertility preservation available to cancer patients, neither of which are tailored to AYA women.<sup>37</sup> This could inform clinical conversations and survivorship needs, but also potential relationships between pretreatment individual differences and later outcomes.

Although more AYA women seem to be engaging in discussions with their oncologists about the risk of fertility loss

and fertility preservation options, likely due to the publication of clinical guidelines from societies such as ASCO,<sup>36</sup> a significant number are not being provided with the information they desire and are not making fully informed treatment decisions.<sup>20,22</sup> Despite advances in fertility preservation methods for women, male AYA patients are still more likely to receive information about fertility preservation options and more likely to utilize them.<sup>44,45</sup> The impact of gender discordance in the patient-provider dyad may also make discussing fertility preservation options more difficult for some patients.<sup>20</sup> Providers and care teams make more immediate impact by providing information to AYA women, referring them to fertility preservation consultations, and starting the discussion early and openly. Prior findings suggest that these actions should be taken as early in the treatment planning phase as possible to allow patients to digest the risk of fertility loss and have as much time as possible to make informed decisions.<sup>18</sup> Fully informed decisions that occur as early as possible may also decrease anticipated regret and increase perceived control over uncertainty for patients who may otherwise choose to achieve this by pursuing fertility preservation, possibly delaying treatment to their detriment in the process. Future studies of shared decision-making about fertility preservation should include measures of psychosocial constructs such as these to elucidate the importance of perceived involvement in decision-making. In addition, further study of the impact of treatment delays due to fertility preservation is needed in diverse settings.<sup>9</sup> As patients progress to survivorship, regardless of their fertility preservation treatment decision, care

teams should continue to monitor fertility outcomes of AYA women and provide them information regarding family planning to protect against further distress, especially as the extent of damage to fertility due to treatment is often uncertain.<sup>19,46</sup>

## Future Directions

Fertility is a top priority for AYA women undergoing cancer treatment with long term impacts on psychosocial and emotional wellbeing. Further study of the fertility preservation decision-making process will aid in ensuring patients are making fully informed decisions, as well as in intervention development to lessen decisional conflict before treatment and alleviate regret after treatment and into long-term survivorship. For providers to fully inform their patients of infertility risk, clinical and longitudinal data regarding fertility outcomes of AYA women cancer survivors are needed.

When deciding on a treatment plan, providers should discuss risks to female fertility and sexual function concurrently with the likelihood of remission and survival, with prompt referral to fertility specialists regardless of the initial perceived threat and priority of fertility. By adequately addressing fertility with the same urgency and precision as the underlying cancer through shared decision-making tools, we will continue to move toward a more patient-centered model of total cancer care. ■

**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..

➤ For full reference list, visit [cancernetwork.com/AYA\\_fertility](http://cancernetwork.com/AYA_fertility)



### Allen

is an assistant professor, Department of Hematology and Medical Oncology,

Emory University Winship Cancer Institute, Atlanta, Georgia.



### Payne

is a doctoral student, Department of Psychology, Stony Brook University, Stony Brook, New York.



### Flowers

is chair of the Department of Lymphoma/Myeloma at the University of Texas MD Anderson

Cancer Center.





## PERSPECTIVE BY

Elizabeth S. Constance, MD

## Opening Doors: Fertility Preservation for Adolescents and Young Adults Facing Gonadotoxic Therapy

**A**s long-term survival rates continue to rise in adolescents and young adults (AYAs) receiving a diagnosis of cancer, the focus of oncologic care has shifted from survival to both survival and quality of life after treatment. For many individuals in the AYA age group (defined as ages 15-39), a commonly cited survivorship concern is reproductive function and the ability to have biological children in the future.<sup>1</sup> Unfortunately, cancer and cancer-related therapies can have a significant detrimental impact on future fertility and reproductive function in both men and women of reproductive age. The threat to reproductive function in women following cancer therapy is 2-fold: first, gonadotoxic therapies can lead to complete gonadal failure, characterized by premature ovarian insufficiency, or early menopause, which has long-term implications for bone and cardiovascular health as well as cognitive function. Second, even for those individuals who do not experience complete gonadal failure, most will experience impaired fertility to some degree, including shortening of the reproductive window.<sup>2</sup> Resources for estimating the reproductive risk of common cancer-related therapies are available<sup>3</sup>, which can help clinicians counsel patients regarding these risks and facilitate timely referral to a reproductive specialist prior to initiating fertility-threatening treatment when feasible and desired.

Multiple studies have shown that an infertility diagnosis has the same psychological impact on an individual as a cancer diagnosis.<sup>4-5</sup> Therefore, AYAs with a new cancer diagnosis requiring fertility-threatening therapy are often faced with the double-hit of receiving these diagnoses simultaneously. This double diagnosis and the associated psychosocial repercussions underscore the importance of having discussions with AYA patients with cancer early in the diagnosis process to consider options for fertility preservation prior to cancer treatment. Prompt referral to a reproductive specialist can be invaluable both in terms of providing comprehensive and accurate counseling regarding treatment risks and also allow for pursuing fertility preservation options as quickly as possible so as to minimize any delay in initiating cancer treatment.

There are a variety of fertility preservation methods available to women preparing to undergo potentially gonadotoxic therapy. The most widely available and commonly utilized established fertility preservation method is ovarian stimulation with oocyte or embryo cryopreservation by vitrification. With the development of protocols allowing for the immediate start of ovarian stimulation at any point in a woman's menstrual cycle, the time from consultation with a fertility specialist to oocyte retrieval and cryopreservation can generally be accomplished in approximately

2 weeks. This allows for minimal delays in the initiation of cancer therapy without compromising oocyte yield or quality.<sup>6</sup> Ovarian tissue cryopreservation can be accomplished through surgical removal of all or part of 1 ovary, leaving the other ovary in situ with the goal of preserving future endocrine function. Strips of ovarian cortical tissue are then cryopreserved (either through slow freezing or vitrification) and later retransplanted into the patient at either an orthotopic (ovarian fossa or surface of contralateral ovary) or heterotopic (subcutaneous tissue of the arm or abdomen) location when pregnancy is desired. Although ovarian tissue cryopreservation is now an established fertility preservation technique and no longer considered experimental,<sup>7</sup> fertility centers able to offer this option remain relatively limited compared with centers that offer other fertility preservation methods. Finally, ovarian suppression using GnRH (gonadotropin-releasing hormone) agonists can be used alone or in conjunction with the other fertility preservation strategies above. This method is still considered experimental due to lack of long-term data on fertility outcomes, however data in patients with breast cancer have been promising.<sup>8-9</sup> This may, however, be the only option for women who require immediate initiation of gonadotoxic therapy and thus cannot wait the time required to undergo ovarian stimulation for

oocyte cryopreservation or surgery for ovarian tissue harvesting.

While expediting referral to reproductive specialists for fertility preservation treatment and procedures increases the number of women who have the opportunity to pursue these treatments, it also condenses the time women and their families have to make these potentially life-changing decisions. This condensed timeline for making high-stakes decisions drives home the importance of having effective tools available to aid in decision-making for these patients and families. Institution of a multidisciplinary program incorporating oncology, reproductive endocrinology, urology, mental health professionals, genetic counselors, and other specialists involved in the patient's care improves both utilization of fertility preservation methods and patient satisfaction even when no fertility preservation treatment is sought.<sup>10-12</sup> Having a member of the multidisciplinary care team who serves as a patient navigator, providing initial education about fertility risks and preservation options as well as connecting patients and families with the appropriate specialist referrals, aids in standardizing the patient experience. The goal of the patient navigator is to ensure that all patients are receiving consistent, accurate, and timely information, which can decrease feelings of overwhelm while helping patients and families feel empowered in their decision-making, ultimately reducing feelings of regret later.

For AYA patients and their families, facing a new cancer diagnosis can be incredibly overwhelming both in the breadth and depth of information they receive and the need to quickly make decisions

regarding life-saving treatment. As these patients are increasingly becoming long-term cancer survivors, survivorship issues such as fertility and reproductive function are gaining in importance among patients, families, and health care providers. Providing information and timely referral to a reproductive specialist can help preserve future fertility and improve reproductive function following cancer treatment, but can also increase information overload and decisional uncertainty at the time of diagnosis. Ongoing development of tools to assist patients and families in making these complex decisions, as well as the incorporation of fertility preservation specialists into multidisciplinary care teams, are likely to decrease decisional regret and improve patient satisfaction. ■

**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.

#### REFERENCES

1. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer: A pilot survey of survivors' attitudes and experiences. *Cancer*. 1999;86(4):697-709. doi:10.1002/(sici)1097-0142(19990815)86:4<697::aid-cncr20>3.0.co;2-j
2. Partridge AH, Ruddy KJ, Gelber S, et al. Ovarian reserve in women who remain premenopausal after chemotherapy for early stage breast cancer. *Fertil Steril*. 2010;94(2):638-644. doi:10.1016/j.fertnstert.2009.03.045
3. Livestrong Foundation. Fertility risks for women. Accessed October 31, 2020. [https://prod-io.livestrong.org/sites/default/files/rs/images-email/pdfs/livestrong-fertility/LF\\_FertilityRiskCharts\\_Women.pdf](https://prod-io.livestrong.org/sites/default/files/rs/images-email/pdfs/livestrong-fertility/LF_FertilityRiskCharts_Women.pdf)
4. Nieman CL, Kinahan KE, Yount SE, et al. Fertility preservation and adolescent cancer patients: lessons from adult survivors of childhood cancer and their parents. *Cancer Treat Res*. 2007;138:201-217. doi:10.1007/978-0-387-72293-1\_15
5. Tschudin S, Bitzer J. Psychological aspects of fertility preservation in men and women affected by cancer and other life-threatening diseases. *Hum Reprod Update*. 2009;15(5):587-597. doi:10.1093/humupd/dmp015
6. Kuang Y, Hong Q, Chen Q, et al. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. *Fertil Steril*. 2014;101(1):105-111. doi:10.1016/j.fertnstert.2013.09.007
7. Practice Committee of the American Society of Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: A committee opinion. *Fertil Steril*. 2019;112(6):1022-1033. doi: 10.1016/j.fertnstert.2019.09.013
8. Del Mastro L, Boni L, Michelotti A, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA*. 2011;306(3):269-276. doi:10.1001/jama.2011.991
9. Moore HC, Unger JM, Phillips K, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. 2015;372(10):923-932. doi:10.1056/NEJMoa1413204
10. Kelvin JF, Thom B, Benedict C, et al. Cancer and fertility program improves patient satisfaction with information received. *J Clin Oncol*. 2016;34(15):1780-1786. doi:10.1200/JCO.2015.64.5168
11. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer*. Published online September 1, 2011. doi:10.1002/cncr.26459
12. Srikanthan A, Amir E, Warner E. Does a dedicated program for young breast cancer patients affect the likelihood of fertility preservation discussion and referral? *Breast*. 2016;27:22-26. doi:10.1016/j.breast.2016.02.012

**Constance** is an assistant professor, Department of Obstetrics and Gynecology, University of Nebraska Medical Center.

# FDA Approves Nivolumab Plus Ipilimumab for Previously Untreated Unresectable Malignant Pleural Mesothelioma

Kevin Wright

**T**he FDA approved nivolumab (Opdivo) in combination with ipilimumab (Yervoy) for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM), according to Bristol Myers Squibb.

The approval was based on efficacy results from a pre-specified interim analysis from the open-label, multi-center, randomized phase 3 CHECKMATE 743 (NCT02899299) trial, designed to evaluate nivolumab plus ipilimumab compared with chemotherapy (pemetrexed and cisplatin or carboplatin) in patients with histologically confirmed unresectable MPM and no prior systemic therapy or palliative radiotherapy within 14 days of initiation of therapy.<sup>1</sup>

With a minimum of 22.1 months of follow-up, the immunotherapy combination demonstrated superior overall survival (OS), compared with the standard chemotherapy arm (HR, 0.74; 95% CI, 0.61-0.89;  $P = .002$ ), with a median OS of 18.1 months (95% CI, 16.8-21.5) versus 14.1 months (95% CI, 12.5-16.2), respectively. Two-year OS was 41% with nivolumab plus ipilimumab, compared with 27% with chemotherapy.<sup>1,2</sup>

A total of 303 patients were randomized to receive 3 mg/kg nivolumab every 2 weeks and 1 mg/kg ipilimumab every 6

weeks, while 302 patients were randomized to receive 75 mg/m<sup>2</sup> cisplatin or 500 mg/m<sup>2</sup> carboplatin area under the curve 5 plus pemetrexed in 3-week cycles for 6 cycles until disease progression or unacceptable toxicity or, in the combination arm, up to 24 months.

The primary end point was OS in all randomized patients. Secondary end points included progression-free survival (PFS), objective response rate (ORR) and duration of response (DOR).

Median PFS for the immunotherapy arm, per blinded independent central review (BICR), was 6.8 months (95% CI, 5.6-7.4) and 7.2 months (95% CI, 6.9-8.1) in the standard chemotherapy arm (HR 1.0; 95% CI, 0.82-1.21). Confirmed ORR per BICR was 40% (95% CI, 34%-45%) and 43% (95% CI, 37%-49%) in the nivolumab plus ipilimumab and chemotherapy arms, respectively. Median DOR was 11.0 months for patients receiving the immunotherapy combination compared with just 6.7 months in the chemotherapy arm.

Although the interim analysis from CHECKMATE 743 showed improvements in survival rates in both nonepithelioid and epithelioid malignant pleural mesothelioma, patients with a nonepithelioid histology derived the larger benefit.

Median OS for this subgroup was 18.1 months (HR, 0.46; 95% CI, 0.31-0.68) with the dual immunotherapy combination compared with 8.8 months for those patients receiving standard chemotherapy. At 24 months, OS was 38% for those patients with nonepithelioid histology who received the immunotherapy combo, versus 8% for those receiving the standard chemotherapy treatment.<sup>3</sup>

In the immunotherapy arm, 23% of patients discontinued treatment due to adverse events (AEs) and 52% had at least 1 dose withheld for an AE. Moreover, 4.7% of patients permanently discontinued ipilimumab alone due to AEs. The most frequent grade 3/4 AEs included pneumonia, pyrexia, diarrhea, pneumonitis, pleural effusion, dyspnea, acute kidney injury, infusion-related reaction, musculoskeletal pain, and pulmonary embolism.<sup>2</sup>

This approval represents the first and only immunotherapy treatment approved for this patient population and comes 6 weeks after the submission of a new supplemental biologics license application.<sup>2</sup> ■

**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.

➤ For full reference list, visit [cancernetwork.com/FDA\\_MPM](http://cancernetwork.com/FDA_MPM)

## COMMENTARY

**Marjorie G. Zauderer, MD***Co-Director, Mesothelioma Program, Memorial Sloan Kettering Cancer Center*

**T**here has not been new treatment regimen approved for mesothelioma in over 15 years. This was desperately needed for so many patients. To have another option, particularly up front, when patients are at their healthiest and best able to tolerate treatment is great. We've seen immunotherapy really come into primetime for lots of other malignancies, and it's nice to see it come forward for a less common disease like mesothelioma.

With these types of treatments, the devil is always in the details. For certain subtypes of mesothelioma—sarcomatoid and biphasic—the data show that the combination of ipilimumab (Yervoy) and nivolumab (Opdivo) seemed to lead to better outcomes than cisplatin and pemetrexed.

That difference is much smaller in patients with epithelioid mesothelioma, however.

Often, and particularly in the United States, we'll give 3 chemotherapy agents for epithelioid disease, and the trial only compared nivolumab and ipilimumab with 2 chemotherapy agents. When you factor that in as well, again, the difference is smaller. So, in terms of how we implement this in our practice, there are still some questions. But certainly, using immunotherapy is a highly effective way of treating patients, and it spares them the toxicities of chemotherapy. Many toxicities like fatigue and nausea, can be so difficult for people going through traditional chemotherapy.

**Interview: Hitting a New Target in Multiple Myeloma**

Continued from page 489

**Q:** Do you see a common clinical development theme across all hematologic malignancies, like some trend that's coming to the forefront no matter which cancer type you're talking about?

**LONIAL:** There are 2 developing trends that I think are important. While I think many of us in the field would argue that immunotherapy was first invented in hematologic malignancies, with allogeneic transplant for instance, we have learned to refine that a little, particularly by using cellular therapies such as CAR T cells and other ways to augment cellular therapy in all hematological malignancies. I think the second trend is taking the explosion of precision medicine in solid tumor oncology and beginning to apply some of those lessons to hematological malignancies as well. We know that in acute leukemia, for instance, we're beginning to look at certain mutations and treat them differently. We know that in myeloma, we're starting to test precision medicine-based approaches as well. We're also using genetics and genomics to identify lymphoma subsets. That's getting us into

both an immune era and a precision medicine era. And as I said at SOHO [the Society of Hematology Oncology annual meeting], the challenge now for us is marrying the 2 concepts. How do you take both precision medicine and immune therapy and make it a 1-treatment approach for a patient?

**Q:** You're a co-chair of the 25th Annual International Congress on Hematologic Malignancies®, which is devoting a full afternoon session to advances in CAR T-cell therapy. What can we expect from that session?

**LONIAL:** What you will see there is the current state of the art as well as the future state of the art. The current state of the art is really important, because while CAR T-cell therapies are not given in the community oncology practice, knowing when to refer from the community practice for a CAR T-cell treatment, and what that treatment can offer patients, is critically important. That's why it's important to know where we are today. The future, to me, is really exciting, because I think it suggests we can take

diseases that are treatable and potentially cure a larger fraction of them.

**Q:** Do you see CAR T-cell therapy becoming more accessible to the community practice over time?

**LONIAL:** A lot of that depends on the regulations that go along with administering treatment. Right now, you have to be FACT (Foundation for the Accreditation of Cellular Therapy)-accredited to get CAR T cells, which means [that treatment locations] are going to be limited to transplant centers. There probably are going to be opportunities for large community practices at some point to [become accredited] and be able to [administer treatment]. But at least for now, I think that it's not quite ready for prime time. The advantage [of CAR T-cell therapy] from my perspective is it is a one-and-done therapy. And if that one-and-done really is done, then it's a true victory. I think that opportunity for patients is one that we don't want to limit just to people who are seen in academic centers. ■

**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.



# Update on the Treatment of Heavily Pretreated, Relapsed Refractory Multiple Myeloma

## KEY TAKEAWAYS

1. Relapsed refractory multiple myeloma (RRMM) is challenging to treat, and overall survival rates remain low with available therapeutic regimens.
2. Novel treatment targets are under investigation in the search for less toxic and more effective treatments for patients with RRMM.
3. B-cell maturation antigen (BCMA) is a promising therapeutic target. Data from published and ongoing trials suggest that anti-BCMA antibody-drug conjugates may be particularly beneficial for heavily pretreated patients with RRMM.

**M**ultiple myeloma is the second most common hematologic malignancy in the United States, accounting for approximately 17% of all blood cancers.<sup>1</sup> It is characterized by unchecked production of monoclonal plasma cells in the bone marrow, leading to high levels of dysfunctional (monoclonal) immunoglobulins in the blood and urine.<sup>2,3</sup> According to recent estimates, more than 32,000 individuals will be diagnosed with multiple myeloma in the United States in 2020.<sup>4</sup> Therapeutic advances over the last decade have led to prolonged survival, but the prognosis remains poor and the disease is incurable.<sup>5</sup> In an interview with *CancerNetwork*®, Cesar Rodriguez Valdes, MD, clinical assistant professor of Hematology and Oncology at Wake Forest University School of Medicine and a myeloma specialist at the Wake Forest Baptist Comprehensive Cancer Center in Winston-Salem, North Carolina, commented on the impact of new therapies for patients with multiple myeloma. “Historically, multiple myeloma has been a disease that is hard to treat,” he said.

“Previously we had very few treatment options, which had a lot of [adverse] events (AEs) and little efficacy, so the overall survival [rate] of patients was pretty grim,” Rodriguez said. “On average, people could live up to 3 years with the treatments that we had about 15 years ago. Over the last 10 to 15 years, there has been a large number of drugs that have been approved for treatment in multiple myeloma that are very effective at controlling the disease and also have decreased AEs compared [with] the old treatments that we used for myeloma. This has translated into better responses and better control of the disease. Before, while patients would live on average up to 3 [additional] years, now the average is approximately 5 years based on SEER [Surveillance, Epidemiology, and End Results] data.”<sup>6</sup>

The course of multiple myeloma is heterogeneous, but relapse and disease progression are inexorable features of the disease for most patients.<sup>7</sup> Multiple relapses are common and lead to relapsed/refractory multiple myeloma (RRMM). Over the course of repeated re-

lapses, resistant clones emerge that contribute to shorter periods of remission and reduced response (or resistance) to standard salvage therapies.<sup>5,7,8</sup> Patients with RRMM who have failed multiple prior therapies are becoming more common and more challenging to treat, according to Rodriguez, who described the challenge of treating this patient population: “In myeloma, we know that the disease tends to come back, and every time the disease comes back, it tends to be more aggressive and harder to treat. Each time we control this disease, the time we have it controlled tends to shrink as the disease comes back over and over again. We have patients currently who have had 4 relapses, 5 relapses, 6 relapses, or [who] have had many different lines of therapy to try to control the disease. Whenever we deal with [someone] who has heavily pretreated myeloma or who has undergone multiple lines of therapy—more than 4 prior lines of therapy—then we are dealing with a unique situation where we are starting to run out of the drugs that we normally [use] to treat multiple myeloma.”

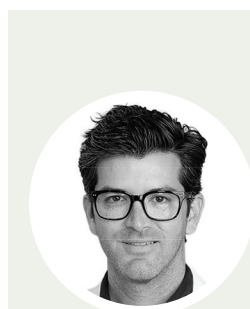
The general approach to treating RRMM is to use doublet or triplet regimens that include some combination of a proteasome inhibitor (PI) (eg, bortezomib, carfilzomib, ixazomib), an immunomodulatory drug (IMiD) (eg, lenalidomide, pomalidomide), and a monoclonal antibody (mAb) (eg, daratumumab, elotuzumab), usually on a dexamethasone backbone, and autologous stem-

cell transplantation in eligible patients.<sup>1</sup> Other treatment approaches, such as CAR-T cell therapy, are in development. Within the last several years, the treatment paradigm for RRMM has changed to one in which patients can be treated at each relapse phase, resulting in prolonged survival.<sup>8</sup>

Selinexor is specifically indicated for patients with heavily pretreated disease. Selinexor is indicated in combination with dexamethasone in adult patients with RRMM who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb.<sup>1,9</sup> It has a novel mechanism of action in that it selectively inhibits nuclear transport of tumor suppressor proteins, glucocorticoid receptors, and oncoprotein mRNAs by exportin 1 (XPO1). XPO1 overexpression in myeloma cells is associated with poor prognosis (ie, shorter overall survival).<sup>10</sup> Rodriguez explained that clinical trials have shown favorable results with selinexor as part of a combination regimen in patients who have received 4 or 5 prior therapies.<sup>10</sup> “[In the STORM trial,] selinexor in combination with dexamethasone had an overall response rate of approximately 26%.<sup>10</sup> Even though this number seems to be low, we need to keep in mind that these are patients who have been heavily pretreated and who are refractory or who have been exposed to the most common agents that we normally use for multiple myeloma. (These include bortezomib or carfilzomib, lenalidomide, pomalidomide and daratumumab.) [Therefore,] seeing a response such as this in [a patient] who has had this [high] amount of therapy in the past is actually a very promising thing. When we combine it with other agents, we are seeing preliminary data that actually increase this response rate up to 60% or higher.”<sup>11</sup>

### Novel Treatment Targets for RRMM

There have been ongoing efforts to iden-



### Expert Interview With Cesar Rodriguez Valdes, MD

Rodriguez discusses the rationale for B-cell maturation antigen-targeted novel approaches such as antibody-drug conjugates, bispecific antibodies, and CAR T-cell therapies as treatment for patients with heavily pretreated relapsed/refractory multiple myeloma.



To see the full video with Dr Rodriguez, scan the code.

tify novel treatment targets for RRMM, with the goal of developing more effective therapies with fewer AEs. A novel target that has recently been the subject of considerable attention is the multiple myeloma cell-surface receptor B-cell maturation antigen (BCMA).<sup>12</sup> BCMA is preferentially expressed on multiple myeloma cells and is important to the long-term survival of plasma cells in the bone marrow and can affect disease progression.<sup>5</sup> The level of BCMA expression has been shown to remain stable across the different stages of the disease, from diagnosis through relapse, underscoring its potential as a treatment target.<sup>2,5</sup> Rodriguez discussed the potential of BCMA as a treatment target. “The unique thing about BCMA is that it is highly expressed in myeloma cells, and it is seen in other B-cells; [however,] it is rarely seen in other types of cells [in the body],” he said. “If we identify a therapy that is effective at killing the cells that have the surface antigen, we can reduce the toxicity and zone in on the cells that we want: the myeloma cells. BCMA is a protein that helps modulate B-cell proliferation. It can activate the cells and promote B-cell survival. Whenever you have a myeloma cell that is overexpressing BCMA, this confers to the myeloma cell advantage of survival, proliferation, and activation. If we find a therapy that can actually neutralize that, then we can have better control at the proliferation and the control of the cell survival of that cell.

BCMA has been studied as a target in mAb therapy, antibody-drug conjugate therapy, and CAR T-cell therapy. There are many options that we can use in terms of immunotherapy [that] can focus on BCMA as a target so that we can reduce toxicities and AEs.”

The BCMA-directed antibody and microtubule inhibitor conjugate, belantamab mafodotin, was granted accelerated approval by the FDA in August 2020 for the treatment of patients with RRMM who have received at least 4 prior therapies, including an anti-CD38 mAb, a PI, and an IMiD.<sup>13</sup> Belantamab mafodotin is a first-in-class afucosylated, humanized immunoglobulin G1 anti-BCMA mAb linked with a tubulin polymerization inhibitor, monomethyl auristatin F.<sup>5,12</sup> Upon binding to the BCMA cell surface receptors, belantamab mafodotin leads to multiple myeloma cell death through multiple mechanisms, including apoptosis, cytotoxicity, cellular phagocytosis, and immunogenic cell death.<sup>12</sup> According to Rodriguez, there are some definite advantages to targeting BCMA with an antibody-drug conjugate. “Using an antibody-drug conjugate gives us many benefits in addition to just the mAb,” he said. “The monoclonal antibody part is going to help identify the myeloma cell and it is going to help inhibit the BCMA that is in that myeloma cell that helps with proliferation and survival. At the same time, it is going to help identify the cancer cell by the T cells. But the added benefit is that, in addition to

those things, it is also going to deliver a drug that is in the antibody once it attaches to the BCMA. And that way, you are going to have the drug delivered straight to the cancer cell while also taking the benefit of inhibiting the BCMA and helping the T cells identify the myeloma cells.”

Lonial et al evaluated the efficacy and safety of belantamab mafodotin in patients with RRMM in the DREAMM-2 study (NCT03525678), the results of which were published in *The Lancet* in February 2020. DREAMM-2 was a 2-arm, randomized, open-label, phase 2, international study of adult patients with RRMM. Among other eligibility criteria, patients had disease progression after 3 or more lines of therapy and were refractory to IMiDs and PIs, and refractory and/or intolerant to an anti-CD38 monoclonal antibody. Patients were stratified by number of previous lines of treatment ( $\leq 4$  vs  $> 4$ ) and whether they had high-risk cytogenetic findings, and then randomized in a 1:1 ratio to receive either 2.5 mg/kg or 3.4 mg/kg belantamab mafodotin. They received treatment intravenously once every 3 weeks. The number of cycles was determined by disease progression and/or toxicity. The primary end point was the overall response, defined as the percentage of patients who achieved partial response or better, as assessed by an independent review committee.<sup>12</sup>

Patients in both dose groups had a median of 3 treatment cycles. Thirty of 97 patients (31%) in the 2.5 mg/kg group and 34 of 99 patients (34%) in the 3.4 mg/kg group achieved an overall response. Approximately 20% of patients in each dose group achieved a very good partial response or better. The median duration of response had not been reached at the time of this study's publication. At the time of data cutoff, 18 of 97 and 25 of 99 patients in the 2.5 mg/kg and 3.4 mg/kg groups, respectively, had a duration of response of at least 4 months and were continuing with treatment. The authors estimated a 78% probability of having

**It would be very interesting to see how this therapy is going to make headway as we use it in earlier lines of therapy or earlier in the diagnosis of myeloma and how this is going to impact when we combine it with other agents.**

a similar duration of response in the 2.5 mg/kg group and 87% in the 3.4 mg/kg.<sup>12</sup>

Nearly all patients (98% and 100%) in each group experienced at least 1 AE.<sup>12</sup> Eight percent of patients in the 2.5 mg/kg group and 10% in the 3.4 mg/kg group discontinued treatment indefinitely due to AEs, most commonly keratopathy. AEs of interest were grade 3-4 keratopathy (27% and 21%), thrombocytopenia (20% and 33%), and anemia (20% and 25%, respectively). Rodriguez discussed the important AEs in this study. “Toxicities were something that were somewhat concerning at the beginning because the most common toxicities included eye keratopathy, anemia, thrombocytopenia, and infusion reactions.<sup>12</sup> The eye keratopathy [was] a new AE that we had not normally seen in multiple myeloma therapies,” he said. “It was seen in a good number of myeloma patients [who] were receiving this drug [as were eye blurriness and dryness]. [Keratopathy] is the toxicity that concerned the FDA at the beginning and required the drug company to find ways to mitigate this so that it does not become a serious problem for myeloma patients. Fortunately, after our studies, we have seen that people who do develop any eye symptoms can have reversal of their symptoms if they are closely monitored by an eye specialist. For this reason, people who receive therapy with belantamab mafodotin need to be seen by an eye doctor every 3 weeks prior to each therapy to monitor the cornea of the eye and make sure that there are no toxicities. If there are early signs of toxicities, then the drug can be held or can be dose reduced so that those toxicities do not get

worse. About 20% of the patients [21% at the 2.5 mg/kg dose and 16% at the 3.4 mg/kg dose] developed some infusion-related reaction.<sup>12</sup> For this reason, people need some premedications to try to reduce the risk of [AEs].”<sup>13</sup>

The results of the DREAMM-2 study are encouraging for patients with heavily pretreated RRMM. The efficacy of belantamab mafodotin monotherapy was comparable to the efficacy observed in previous studies with approved combination treatments in this patient population.<sup>12</sup> Data from the 13-month follow-up, recently presented at the 2020 American Society of Clinical Oncology (ASCO) virtual annual meeting, showed a median duration of response of 11 months and a median overall survival of 13.7 months in heavily pretreated patients who received single-agent belantamab mafodotin 2.5 mg/kg.<sup>14</sup>

DREAMM-6 (NCT03544281) is an ongoing, phase 1/2, open-label, dose escalation and expansion study investigating whether adding belantamab mafodotin (2.5 mg/kg) to 1 of the current standard-of-care combination therapies (lenalidomide + dexamethasone or bortezomib + dexamethasone) increases the efficacy observed with monotherapy in DREAMM-2. As of the May 2020 ASCO virtual annual meeting, 18 patients with a median of 3 prior therapies had been treated. The overall response rate was 78%, with 50% of patients achieving a very good partial response.<sup>14</sup> Infusion reactions, thrombocytopenia, and corneal events were the most common AEs at a median of 18.2 weeks of treatment.<sup>15</sup>

When asked to summarize his thoughts about the potential role of belantamab

mafodotin in the treatment of patients with heavily treated RRMM, Rodriguez stated: “This is a game changer in the myeloma world because it expands our armamentarium that we can have to treat myeloma, especially [in] people who have been heavily pretreated, where we are seeing responses by using this drug. It would be very interesting to see how this therapy is going to make headway as we use it in earlier lines of therapy or earlier in the diagnosis of myeloma and how this is going to impact when we combine it with other agents.”

## Conclusions

RRMM is a difficult-to-treat hematologic malignancy with a generally poor prognosis. Advances in treatments and therapeutic approaches over the last decade have extended overall survival, but the 5-year relative survival rate is only 53.9%<sup>6</sup> and more research is urgently needed. Several novel treatment combinations are being explored, as are potential new treatment targets. BCMA is a promising cell-surface receptor preferentially expressed in multiple myeloma cells that plays a key role in their survival. Anti-BCMA therapies, including bispecific antibodies, antibody-drug conjugates, and CAR T-cell therapy, have the potential to change the landscape for patients with RRMM. ■

## REFERENCES

1. Kumar SK, Callander NS, Hillengass J, et al. NCCN guidelines insights: multiple myeloma, version 1.2020. *J Natl Compr Canc Netw*. 2019;17(10):1154-1165. doi:10.6004/jnccn.2019.0049
2. Abramson HN. B-cell maturation antigen (BCMA) as a target for new drug development in relapsed and/or refractory multiple myeloma. *Int J Mol Sci*. 2020;21(15):5192. doi:10.3390/ijms21155192
3. Gerecke C, Fuhrmann S, Striffler S, et al. The diagnosis and treatment of multiple myeloma. *Dtsch Arztebl Int*. 2016;113(27-28):470-476. doi:10.3238/arztebl.2016.0470
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30. doi:10.3322/caac.21590
5. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia*. 2020;34(4):985-1005. doi:10.1038/s41375-020-0734-z
6. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: myeloma. Accessed October 19, 2020. <https://seer.cancer.gov/statfacts/html/mulmy.html>
7. Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia*. 2018;32(2):252-262. doi:10.1038/leu.2017.329
8. Bazarbachi AH, Al Hamed R, Malard F, Harousseau JL, Mohty M. Relapsed refractory multiple myeloma: a comprehensive overview. *Leukemia*. 2019;33:2343-2357. doi:10.1038/s41375-019-0561-2
9. Xpovio. Prescribing information. Karyopharm Therapeutics Inc. Updated June 2020. Accessed September 29, 2020. <https://www.karyopharm.com/wp-content/uploads/2019/07/NDA-212306-SN-0071-Prescribing-Information-01July2019.pdf>
10. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med*. 2019;381(8):727-738. doi:10.1056/NEJMoa1903455
11. Richter J, Madduri D, Richard S, Chari A. Selinexor in relapsed/refractory multiple myeloma. *Ther Adv Hematol*. 2020;11. doi:10.1177/2040620720930629
12. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol*. 2020;21(2):207-221. doi:10.1016/S1470-2045(19)30788-0
13. Blenrep. Prescribing information. GlaxoSmithKline. Updated August 2020. Accessed October 13, 2020. [https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Blenrep/pdf/BLENREP-PI-MG.PDF](https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Blenrep/pdf/BLENREP-PI-MG.PDF)
14. DREAMM-2 and DREAMM-6 data at ASCO reinforce the potential of GSK's investigational belantamab mafodotin in patients with relapsed/refractory multiple myeloma. News release. GlaxoSmithKline. May 27, 2020. Accessed October 12, 2020. <https://www.gsk.com/en-gb/media/press-releases/dreamm-2-and-dreamm-6-data-at-asco-reinforce-the-potential-of-gsk-s-investigational-belantamab-mafodotin/>
15. DREAMM-6: evaluating belantamab mafodotin and bortezomib plus dexamethasone in relapsed/refractory myeloma. ASH Clinical News. July 15, 2020. Accessed October 1, 2020. <https://www.ashclinicalnews.org/on-location/other-meetings/dreamm-6-evaluating-belantamab-mafodotin-bortezomib-plus-dexamethasone-relapsed-refractory-myeloma/>

# We Are Oncology.



Peer review and perspective. More context—deeper insight. Explore us online.



# CONTINUING MEDICAL EDUCATION (CME)

## Progress and Challenges in Non-small Cell Lung Cancer and Colorectal Cancer With Pan-KRAS Inhibitors



### FACULTY

**Jonathan W. Riess, MD, MS**  
Associate Professor of Medicine  
Department of Internal Medicine  
Division of Hematology & Oncology  
UC Davis Comprehensive Cancer  
Center  
Sacramento, California

This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

### CME PROVIDER CONTACT INFORMATION

Physicians' Education Resource®, LLC  
2 Clarke Drive, Suite 110  
Cranbury, NJ 08512  
Toll-Free: 888-949-0045  
Local: 609-378-3701  
Fax: 609-257-0705  
info@gotoper.com



### LEARNING OBJECTIVES

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

- Explain the differences between pan-KRAS and selective KRAS inhibition and how this could affect clinical activity
- Evaluate efficacy and safety from clinical trials of pan-KRAS inhibitors in NSCLC and CRC
- Describe the rationale for using pan-KRAS inhibitors individually and in combination for treating NSCLC and CRC

**RELEASE DATE:** November 1, 2020

**EXPIRATION DATE:** November 1, 2021

### INSTRUCTIONS FOR PARTICIPATION / HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to <https://www.gotoper.com/go/onc-nsclc20colorectal> to access and complete the posttest.
3. Answer the evaluation questions.
4. Request credit using the drop-down menu.

**You may immediately download your certificate.**

### FACULTY, STAFF, AND PLANNERS' DISCLOSURES

In accordance with ACCME Guidelines, PER® has identified and resolved all COI for faculty, staff, and planners prior to the start of this activity by using a multistep process.

**Disclosures (Dr. Jonathan Riess):** *Grant/Research Support:* Merck, Novartis, Spectrum, Revolution Medicine, AstraZeneca. *Consultant:* Novartis, Boehringer Ingelheim, Medtronic, Blueprint.

The staff of PER® have no relevant financial relationships with commercial interests to disclose.

### OFF-LABEL DISCLOSURE AND DISCLAIMER

This activity may or may not discuss investigational, unapproved, or off-label use of drugs. Learners are advised to consult prescribing information for any products discussed. The information provided in this activity is for accredited continuing education purposes only and is not meant to substitute for the independent clinical judgment of a healthcare professional relative to diagnostic, treatment, or management options for a specific patient's medical condition. The opinions expressed in the content are solely those of the individual faculty members, and do not reflect those of PER® or any of the companies that provided commercial support for this activity.

**This activity is funded by PER®.**

### ACCREDITATION/CREDIT DESIGNATION

Physicians' Education Resource®, LLC, is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. Physicians' Education Resource®, LLC, designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**G**enomic alterations involving the *RAS* family of genes are the most prevalent driver mutations implicated in cancer and are present in approximately 25% to 30% of tumors.<sup>1,2</sup> Among *RAS* isoforms, mutations in the *KRAS* oncogene are the most common, accounting for approximately 85% of *RAS*-driven cancers. Until recently, *KRAS* was considered an undruggable target in the development of novel therapies for patients with cancers harboring *KRAS* mutations. Research efforts in targeting mutant *KRAS* have undergone a resurgence following the discovery of a potentially targetable region on the *KRAS* protein.<sup>3</sup> Additional strategies in targeting *KRAS*-mutant tumors, particularly non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), include inhibiting both upstream and downstream *KRAS* signaling processes.

Jonathan W. Riess, MD, MS, reviews the role of mutated *KRAS* protein in tumor progression and recent developments regarding emerging novel agents designed to target mutant *KRAS* activity in patients with NSCLC and CRC.

**Q: What is the physiological function of *KRAS*?**

**RIESS:** The *KRAS* gene provides instructions for the *KRAS* protein that is a component of the signaling pathway known as the *RAS*/*RAF*/*MAPK* pathway, which relays signals to the cell nucleus

that instruct the cell to grow, proliferate, mature, and differentiate.<sup>4</sup> The *KRAS* protein is involved in the regulation of cell division as a result of its ability to relay external signals to the cell nucleus. Physiologically, *KRAS* switches between an activated and inactivated state when bound to GTP and GDP, respectively.<sup>5</sup> Dimerization of *KRAS* at the membrane level leads to activation of downstream signaling pathways, and these include the *MAPK* pathway, which impacts proliferation; the *PI3K* pathway, which impacts cell survival; and the *RAL*-*GEF* pathway, which impacts cytokine production.<sup>6</sup>

**Q: How prevalent are *KRAS* mutations across different forms of cancers?**

**RIESS:** *KRAS* mutations are prevalent among multiple tumor types. They occur in about 25% of all cancers.<sup>1,2,7</sup> *KRAS* represents about 86% of *RAS* mutations.<sup>7</sup> The most common mutations are in codons 12, 13, and 61.<sup>8</sup> *KRAS* mutations comprise 30% to 50% of all CRC and have a negative predictive value for response to *EGFR* monoclonal antibody therapy.<sup>9</sup> Similarly, *KRAS* mutations comprise about 20% of NSCLC and nearly 100% of all pancreatic adenocarcinomas.<sup>7</sup> Depending on the tumor type, the frequency of amino-acid substitution of the *KRAS* mutation is quite variable. In NSCLC, for example, *KRAS* G12C mutations represent approximately half of all *KRAS* mutations.<sup>10</sup>

**“*KRAS* mutations are prevalent among multiple tumor types. They occur in about 25% of all cancers.”**

—Jonathan W. Riess, MD, MS

In NSCLC, transversion mutations (ie, substitution of a purine nucleotide with a pyrimidine or vice-versa) are more common in patients with a history of heavy smoking, whereas transition mutations (ie, substitution of a purine with a purine or pyrimidine with a pyrimidine), such as G12D, are more common in never-smokers.<sup>11</sup> The G12C mutation is less common in CRC, whereas G12B is more common. Lastly, pancreatic adenocarcinoma has a much lower frequency of G12C mutations, which impacts the effectiveness of some direct-inhibitor therapies to *KRAS* G12C, which we will discuss later.<sup>12</sup>

**Q: What are the major co-occurring mutations that accompany *KRAS*-mutant NSCLC and CRC? Do different *KRAS* mutations have different co-occurring mutations? How do these co-occurring mutations impact prognosis and treatment of NSCLC and CRC?**

**RIESS:** Our understanding of

*KRAS* co-mutations has rapidly evolved in recent years. In some cancers, co-mutations associated with *KRAS* include tumor suppressors, such as *TP53* and *LKB1* (*STK11*).<sup>13</sup> Recent retrospective data suggest that patients with co-mutations in *KRAS* and *STK11* may have a “colder” immune microenvironment, which renders them less responsive to immunotherapy, although this has not yet been clearly proven.<sup>14</sup>

Another *KRAS* co-mutation is *KEAP1*, which is a negative regulator of the *NRF2* pathway, which may be actionable due its dependence on metabolic processes, such as glutamine metabolism.<sup>15</sup> There are also functional *ARID1A* mutations. These co-mutations in the *ARID1A* gene provide instructions for making a protein that impacts chromatin remodeling, and emerging data suggest that these mutations may render patients more sensitive to immunotherapy; however, this has not been conclusively proven.<sup>16</sup> *ARID1A* mutations also tend to segregate with *KRAS* mutations associated with heavy smoking, such as

G12C.<sup>17</sup> We are learning more about these co-mutations, particularly in NSCLC, and this may impact KRAS-directed treatment along the signaling axis, as well as treatment with immunotherapy and other therapies. This is an exciting aspect of research in KRAS-mutant NSCLC. In CRC, KRAS mutations tend to be mutually exclusive of other oncogene-driver mutations, such as *HER2* and *BRAF*.<sup>18</sup> We are also learning more about targeted therapies along that axis as well.

**Q:** What makes **KRAS** mutations difficult to target in terms of development of an effective therapeutic agent?

**RIESS:** KRAS mutations were one of the first oncogene drivers discovered in cancer in the 1980s, yet we have no effective therapies that target KRAS, although there are some exciting drugs in clinical development, such as the direct KRAS G12C inhibitors.<sup>3</sup> In terms of direct inhibitors, the challenge has been due to the fact that RAS proteins did not initially appear to present suitable pockets to which drugs could bind except for the GDP-to-GTP binding site. Unfortunately, RAS proteins bind tightly to these nucleotides with picomolar affinities and very slow off rates, making the prospect of identifying competitive nucleotide analogs challenging.

Subsequently, researchers developed a tethering approach methodology to screen ligands that bind to targeted

site proteins via a disulfide tether, where native KRAS G12C or an introduced cysteine can capture the ligands.<sup>3</sup> This allowed for the screening of inhibitors to KRAS G12C, which helped identify small molecules that irreversibly bound to the mutant reactive cysteine at codon 12 and enabled the discovery of a previously unappreciated binding pocket near the KRAS effector region. Small molecules binding to this pocket can inhibit KRAS by locking the protein in its GDP-bound and inactive state. Regarding designing effective downstream targets in addition to direct inhibitors, while there are many downstream pathways that are activated by KRAS, there are many inhibitory feedback loops as well.

**Q:** What are some of the recent strategies being explored in developing a KRAS inhibitor?

**RIESS:** Several exciting strategies are being explored in the development of KRAS inhibitors. These include direct KRAS G12C inhibitors, which have demonstrated clinical activity in early stage clinical trials; phase 2/3 trials are currently enrolling patients to evaluate agents that target other KRAS amino acid substitutions, including KRAS G12D.<sup>3</sup> For example, in September 2019, the FDA granted AMG 510, a direct KRAS G12C inhibitor, fast-track designation for the treatment of patients with previously treated metastatic NSCLC harboring

KRAS G12C mutations.<sup>19</sup> The designation was based on follow-up data from a phase 1 trial that was presented at the 2019 WCLC in Barcelona, Spain, and showed objective response rates in patients with NSCLC of about 50%.<sup>20</sup>

**Q:** What are some recent key data regarding the development of direct KRAS inhibitors?

**RIESS:** At the ASCO Annual Meeting this year, data were presented from the Code-Break 100 study, which evaluated AMG 510 in patients with solid tumors other than NSCLC harboring KRAS G12C mutations, and included CRC.<sup>21</sup> Among the 19 patients evaluable for response, there were only 3 responses. More data need to be gathered, but the clinical activity of drugs such as AMG 510 appears to differ in NSCLC versus CRC with KRAS G12C mutations. Furthermore, these differences may be influenced by co-mutations, tumor microenvironment, and tumor location. Specifically, for NSCLC, we are still learning which co-mutations, such as *STK11*, *KEAP1*, *ARID1A*, and *TP53* may influence response to these KRAS G12C direct inhibitors. We are also learning more about the duration of response for progression-free survival, and data for that will be gathered in larger clinical trials. Other KRAS G12C inhibitors in development include MRTX849 and JNJ-74699157.<sup>19</sup> To date, MRTX849 has shown responses in clinical trials,

particularly in patients with NSCLC.<sup>22</sup>

**Q:** What are some recent key data regarding the development of indirect KRAS inhibitors?

**RIESS:** In addition to the exciting developments for direct inhibitors of KRAS G12C, groundbreaking research is evaluating indirect KRAS inhibitors impacting downstream signaling pathways for KRAS-mutant NSCLC. For example, the drug BI 1701963 binds to SOS1 and inhibits KRAS activation by blocking nucleotide exchange for GTP.<sup>23</sup> This is expected to be active in KRAS mutations beyond G12C. A phase 1 trial is evaluating BI 1701963 both as a monotherapy and in combination with the MEK inhibitor trametinib in patients with cancers harboring KRAS mutations. The primary end point is maximum tolerated dose and recommended phase 2 dose, and the target accrual is 140 patients.

Another exciting class of drugs is the SHP2 inhibitors. One agent in early phase development is RMC-4630.<sup>24</sup> RMC-4630 is an oral inhibitor of protein tyrosine phosphatase nonreceptor Type 11, also known as SHP2, and has potential anticancer activity. RMC-4630 targets, binds to, and inhibits the activity of SHP2, which prevents SHP2-mediated signaling impacting MAPK signaling, preventing the growth of SHP2-expressing tumor cells.

Another exciting development is a clinical trial target-

**TABLE 1. Select Clinical Trials Evaluating KRAS Inhibition Agents**

Drug(s)	Mechanism	Clinical trial	Study population
<b>MRTX849 + TNO155</b>	MRTX849: Direct KRAS G12C inhibitor TNO155: SHP2 inhibitor	NCT04330664	NSCLC, CRC
<b>Selumetinib</b>	MEK inhibitor	SELECT-1 trial	NSCLC
<b>Sotorasib (AMG 510)</b>	Direct KRAS G12C inhibitor	CodeBreak-200	NSCLC
<b>MRTX849</b>	Direct KRAS G12C inhibitor	KRYSTAL-1	NSCLC, CRC
<b>Onvansertib</b>	PLK1 inhibitor	NCT03829410	CRC

ing metabolic vulnerabilities in *KRAS* with co-mutations in *KEAP1*. This phase 1 study is evaluating the combination of an mTOR inhibitor with the glutaminase inhibitor CB-839 and its ability to inhibit glutaminolysis in a cohort of patients who have both *KRAS* and *KEAP1* mutations.<sup>25</sup> This approach targets the NRF2 pathway, where mutations in the negative regulator of NRF2 (*KEAP1*) may provide enhanced glutamine dependence and may be potentially actionable with the glutaminase inhibitor CB-839. An ongoing trial is exploring this hypothesis.

Another agent, onvansertib, which is not directly related to *KRAS*, but it inhibits mitosis by targeting a G2 mitosis checkpoint, which is a master regulator of cell-cycle progression, is being evaluated in *KRAS*-mutant NSCLC.<sup>26</sup> Onvansertib belongs to a class of drugs called polo-like kinase 1 (PLK1) inhibitors, which cause mitotic arrest and cell death. Early phase 1 data were presented at AACR this year and showed that onvansertib in combination with bevacizumab and FOLFIRI chemotherapy as second-line treatment of patients with

CRC harboring *KRAS* mutations elicited some responses.

**Q:** How do you anticipate *KRAS* inhibitors will be integrated into the treatment landscape in managing patients with CRC?

**RIESS:** The role of *KRAS* inhibitors in CRC, including place in therapy, combinations with standard-of-care agents, as well as investigational agents, is an ongoing area of research. More data are needed for *KRAS* G12C–direct inhibitors in patients with CRC, as we need to see if the response rate and clinical activity are comparable with those of NSCLC. For example, in *BRAF*-mutant CRC, there are data with *BRAF* inhibitor, MEK inhibitor, and EGFR monoclonal antibody. Rational combination strategies would result from evaluating these feedback loops and determine how to use direct inhibitors to target vulnerabilities in signaling pathways, including those downstream of RAS/RAF/MAPK. For example, in melanoma and NSCLC, in another *RAF* mutation, the *BRAF* mutation, dabrafenib and trametinib, a *BRAF* inhib-

itor and a MEK inhibitor, are approved for the treatment of melanoma and NSCLC. Several *BRAF*/MEK inhibitor combinations have been approved for melanoma based not only upon targeting the upstream signaling, but also the synergistic targeting of downstream signaling. Future approaches in CRC are likely to focus on targeting those downstream vulnerabilities in a synergistic manner, with the goal of keeping overlapping toxicities manageable.

**Q:** How do you anticipate *KRAS* inhibitors will be integrated into the treatment landscape in managing patients with NSCLC?

**RIESS:** Regarding *KRAS*-mutant NSCLC, the *KRAS* G12C direct inhibitors have demonstrated a robust response that is being explored in later-phase clinical trials. Several combination strategies are being explored. One strategy is to combine *KRAS* inhibitors with inhibitors of other pathways involved in *KRAS* signaling and MAPK signaling, for example, combining *KRAS* inhibitors with MEK inhibitors, such as

trametinib. This strategy essentially involves finding synergy along the signaling axis, including SHP2 inhibition. It will be interesting to see how *KRAS* direct inhibitors impact the immune microenvironment. Combining these agents with the checkpoint inhibitors PD-1, PD-L1, and new checkpoint inhibitors should be an area of active investigation. However, caution is warranted regarding potential side effects; for example, as we were studying EGFR and ALK inhibitors in oncogene-driven cancers, we found that combining TKIs and PD-1 inhibitors potentiated the toxicity of the TKI. We are still learning more about how best to integrate these agents into the therapeutic landscape, providing they are successful.

**Q:** Are there any concerns regarding specific adverse events observed in early testing of *KRAS* inhibitors?

**RIESS:** In the early testing of *KRAS* inhibitors, the adverse events and adverse effects observed were generally tolerable.<sup>27</sup> Adverse effects were mainly gastrointestinal (GI) related, mostly diarrhea.



Fatigue and anemia were also observed. As monotherapy, these agents have generally been shown to be tolerable, but the GI adverse effects, liver function changes, fatigue, and anemia, should be considered.

**Q: What are some novel strategies being investigated as an innovative approach to targeting KRAS mutations either directly or indirectly across solid tumors?**

**RIESS:** Essentially, novel direct inhibitors of KRAS G12C have demonstrated clinical activity. There may be differences by tumor type, microenvironment, and co-mutation. For example, there appears to be more activity in NSCLC than in CRC and other tumors. Combination strategies may be influenced by co-mutation, for example, *STK11*, *TP53*, and *ARID1A* in NSCLC, and those co-mutations may benefit from alternative therapies, such as immunotherapy and chemo-immunotherapy combinations. Once we have larger sets of data and more enrolled patients, we will have a better sense of the potential impact of factors beyond tumor type, such as co-mutations.

If the direct inhibitors work well for KRAS G12C in 1 tumor type, a certain subset of those tumors might derive even more benefit from these drugs. In NSCLC, the approach may expand beyond KRAS G12C, which only affects about half of patients. These approaches may include the development

of KRAS G12D inhibitors, which may also be useful in CRC, pancreatic cancer, and other cancers in which the frequency of KRAS G12C mutations or their impact is lower. Other strategies may include SOS1 inhibition, SHP2 inhibition, and combination strategies targeting vulnerabilities along the RAS/RAF/MAPK signaling axis. For example, the success of dabrafenib and trametinib in BRAF-mutant melanoma and NSCLC could be particularly impactful.

The inhibition of KRAS includes a range of mechanisms of action currently undergoing clinical evaluation. Investigational agents targeting KRAS for the treatment of patients harboring KRAS-mutant tumors are listed in **Table 1**.

**Q: What other solid cancers do you anticipate KRAS inhibitors will be investigated as a potential therapy?**

**RIESS:** Solid cancers that would be impacted by KRAS therapy represent about one fourth of all solid tumors. Therefore, finding therapeutics that can target KRAS, whether they are direct inhibitors, along the signaling pathway, or downstream, may dramatically benefit patients with a range of cancers, from solid tumors to hematologic malignancies. In the future, novel combination strategies that are tolerable and that act along specific vulnerabilities along the KRAS/RAF/MAPK pathway are likely to emerge. Specifically, customizing these

combinations based upon signaling vulnerabilities as well as the tumor microenvironment and location may provide benefit in the future. ■

**KEY REFERENCES**

1. Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible? *Nat Rev Drug Discov*. 2014;13(11):828-851. doi:10.1038/nrd4389
20. Fakih M, Neil OB, Price TJ, et al. Phase 1 study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of AMG 510, a novel small molecule KRASG12C inhibitor, in advanced solid tumors. *J Clin Oncol*. 2019;37(suppl 15):3003. doi: 10.1200/JCO.2019.37.15\_suppl.3003
22. Janne PA, Papadopoulos K, Ou SI, Rybkin II, Johnson ML. A Phase 1 clinical trial evaluating the pharmacokinetics (PK), safety, and clinical activity of MRTX849, a mutant-selective small molecule KRAS G12C inhibitor, in advanced solid tumors. Presented at the 2019 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Boston, MA. October 26-30, 2019. [https://www.mirati.com/wp-content/uploads/2019/10/AACR-NCI-EORTC-Clinical-Data-Presentation\\_Janne\\_October-2019-1-1.pdf](https://www.mirati.com/wp-content/uploads/2019/10/AACR-NCI-EORTC-Clinical-Data-Presentation_Janne_October-2019-1-1.pdf).
23. Gerlach D, Gmachl M, Ramharter J, et al. BI-3406 and BI 1701963: Potent and selective SOS1:KRAS inhibitors induce regressions in combination with MEK inhibitors or irinotecan. *Cancer Res*. 2020;80(suppl 16): Abstract 1091. doi:10.1158/1538-7445.AM2020-1091

► For full reference list, visit <https://www.gotoper.com/gonc-nsclc20colorectal>

# WHAT

# MATTERS

A diagnosis of prostate cancer was life-changing news for over 170,000 people per year

Cutting-edge treatments that are noninvasive so he can enjoy a life-changing trip around the world

**cancernetwork**  
home of the journal ONCOLOGY®

*Oncology*® and *CancerNetwork*® lead the industry with the latest insights from key opinion leaders in oncology through articles, peer perspectives, and interactive content that translates into clinical application for today's practicing oncologist. Timely. Practical. Relevant.

**MJH** life sciences™  
knowledge that matters™

Visit our website today at [www.cancernetwork.com](http://www.cancernetwork.com)

©2020 MJH Life Sciences™.  
All rights reserved. Knowledge That Matters™ is a trademark of MJH Life Sciences™.



# Empowered to be bold.

## We're mastering the art of patient-focused treatment

Our robust investigational pipeline of novel small molecule, biologic, and cellular therapies is focused on both improving outcomes and improving the cancer treatment experience for patients around the world.

Be the first to learn about the latest technology in metastatic breast cancer treatment and beyond at [AthenexOncology.com](https://AthenexOncology.com)



[AthenexOncology.com](https://AthenexOncology.com)



Follow us @AthenexOncology

*A*thēnēx oncology

©2020 Athenex. APD-0227-01-01/20

## 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  $1.0 \times 10^9/L$ , 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 ( $\geq 20\%$ ) 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.**

**References:** 1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. 2. Attal M, Richardson PG, Rajkumar SV, et al; on behalf of the ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107. 3. Data on file. sanofi-aventis U.S. LLC. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.2.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed September 9, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.



IN THE TREATMENT OF RELAPSED REFRACTORY  
MULTIPLE MYELOMA IN COMBINATION WITH Pd

## Achieve Greater Outcomes for Your Patients

The first phase 3 trial of an anti-CD38 mAb in  
combination with Pd vs Pd alone<sup>1</sup>

Median PFS of ~1 year with SARCLISA + Pd<sup>1</sup>

SARCLISA + Pd  
(n=154)

11.53  
months  
mPFS

(95% CI: 8.94, 13.9)

HR=0.596  
(95% CI: 0.44, 0.81)  
P=0.0010

6.47  
months  
mPFS

Pd  
(n=153)

(95% CI: 4.47, 8.28)

A significant increase in responses shown with SARCLISA + Pd<sup>1\*</sup>

SARCLISA + Pd (n=154)		Pd (n=153)
60.4% ORR	P<0.0001	35.3% ORR
31.8% ≥VGPR	~4× increase	8.5% ≥VGPR
35 days	Median time to first response among responders	58 days

\*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<sup>1</sup>
- Infusion time decreases to 75 minutes starting after the second infusion in the absence of IRRs<sup>1</sup>

IRR=infusion-related reaction; mPFS=median progression-free survival.

### 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

IMiD is a registered trademark of Celgene Corporation.

© 2020 sanofi-aventis U.S. LLC. All rights reserved. MAT-US-2016919-v1.0-09/2020

**SARCLISA**<sup>®</sup>  
(isatuximab-irfc)  
Injection for IV use | 500mg/25mL, 100mg/5mL