VIEW INFORMATION AND COMMENTARY FROM A TEAM OF EXPERTS

Patient Care Insights™

An Anti-CD38–based Triplet Regimen for Relapsed or Refractory Multiple Myeloma: Patient Case Review

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Managing Patients After MM Relapse: Choosing Appropriate Therapy for Patients Like Donna

What prognostic factors influence treatment decisions in relapsed or refractory MM, and how can oncologists choose appropriate therapies? How can SARCLISA® (isatuximab-irfc), an anti-CD38 mAb,[1] fit into the treatment plans for patients like Donna?

The IKEMA Trial: Study Design & Patient Population

What is the IKEMA study, and what were the patient baseline characteristics for this trial?

Efficacy & Safety of SARCLISA: Insights From IKEMA

How did the triplet regimen of SARCLISA + Kd perform in the IKEMA trial compared to Kd alone? What insights can we gain from information on PFS, response rates, and safety profiles? How do these findings apply to managing treatment for patients like Donna?

Using SARCLISA in Clinical Practice: Dosing & Administration

How is SARCLISA used in clinical practice, and what are some considerations for dosing and administering SARCLISA?

DONNA* | age 61

- Diagnosed with multiple myeloma 2 years ago
- Received pegylated liposomal doxorubicin, bortezomib, dexamethasone, and lenalidomide first line with lenalidomide maintenance for 18 months
- Presenting to hem/onc clinic for followup after M spike and disease progression

Learn more about Donna on page 3 ▶

*Hypothetical inspired by a typical patient in Dr Berenson's practice. Image is actor portrayal.

CD38=cluster of differentiation 38; Kd=carfilzomib and dexamethasone; mAb=monoclonal antibody; MM=multiple myeloma; PFS=progression-free survival.

INDICATION

SARCLISA is indicated:

- in combination with carfilzomib and dexamethasone (Kd), for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy
- in combination with pomalidomide and dexamethasone (Pd), for the treatment of adult patients with multiple myeloma who have received at least 2 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

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

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

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Many factors influence my treatment decisions for patients with relapsed or refractory multiple myeloma. I believe that treating relapsed multiple myeloma is not necessarily about "more;" it's about being "more specific," which means finding an individualized treatment option. Tumor-related factors such as cytogenetic risk and response to prior treatments should be considered, as well as current effect of myeloma on the patient and impact of myeloma on renal function, blood counts, and bone disease. Patient factors such as age, ECOG performance status, and associated comorbidities should also be considered. SARCLISA, an anti-CD38 mAb that binds to a specific epitope on the surface of myeloma cells, works to enhance immune cell function while directly destroying cancer cells.[1] The approval of SARCLISA in combination with carfilzomib or pomalidomide and dexamethasone provides us with more opportunities to individualize treatment for patients who have relapsed and/or refractory multiple myeloma. **– James R. Berenson, MD**

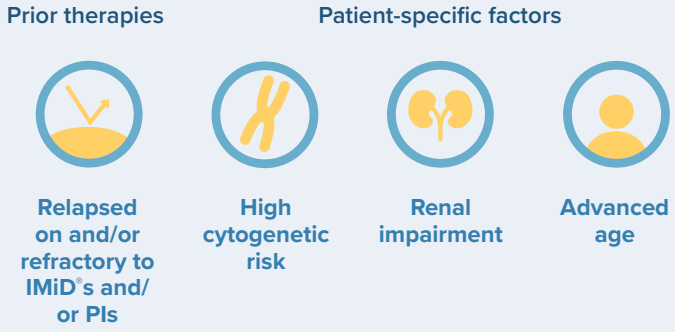
Choosing the Appropriate Therapy for Each Patient at First Relapse Is Imperative

- Patients with multiple myeloma will inevitably relapse, may become refractory to treatment, and experience significantly diminished remission times with subsequent lines of therapy[2,3]
- Additional factors may impact outcomes or limit treatment options for these patients (Figure 1)[2,4,5]
- It's important to choose an appropriate treatment regimen that can extend PFS and deepen responses* for individual patients, including those with poor prognostic factors[2,3]

SARCLISA, a Multimodal Anti-CD38 mAb, Can Be Used as Early as First Relapse[1]

- With SARCLISA, targeted binding to a specific epitope induces distinct antitumor activity.[1,6] SARCLISA:
  - **Directly destroys** myeloma cells through apoptosis without the need for crosslinking[1,7]
  - **Triggers cancer cell death** through tumor cell targeting, including ADCC, ADCP, and CDC[1]
  - **Inhibits CD38** enzymatic activity through suppression of the CD38 ectoenzyme[1,7]
  - **Enhances immune cell function** through NK cell activation and a decrease in immunosuppressors[1]
- SARCLISA, in combination with carfilzomib and dexamethasone (Kd) has been approved as early as first relapse for adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy[1]

Figure 1: Poor Prognostic Factors[a] in Multiple Myeloma[2,4,5]



[a]Poor prognostic factors may include renal insufficiency, older age, high cytogenetic risk, and refractoriness to prior therapies.[4,5]

*A response of ≥VGPR.[8]

ADCC=antibody-dependent cell-mediated cytotoxicity; ADCP=antibody-dependent cellular phagocytosis; CDC=complement-dependent cytotoxicity; IMiD=immunomodulatory drug; NK=natural killer; PI=proteasome inhibitor; VGPR=very good partial response.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Infusion-Related Reactions (cont)

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, 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. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

Neutropenia

SARCLISA may cause neutropenia.

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

Meet Donna, a Patient Appropriate for Therapy With SARCLISA® (isatuximab-irfc) + Kd

*Hypothetical inspired by a typical patient in Dr Berenson's practice. Image is actor portrayal.

Donna* | age 61

- Retired salesperson who normally fills days with yoga, spin class, and gardening
- Has been married for 38 years
- Diagnosed with multiple myeloma 2 years ago
- Presenting to hem/onc clinic for follow up after M spike and disease progression

Donna received pegylated liposomal doxorubicin, bortezomib, and dexamethasone first line. Because of inadequate response, lenalidomide was added during the third cycle, and she achieved a partial response. She was put on maintenance therapy with lenalidomide. After 18 months, she showed signs of a biochemical relapse with worsening renal failure and bone pain. X-rays showed new lytic lesions in her femurs.

Past Medical History

- Hyperlipidemia treated with atorvastatin
- Family history of cancer: father died at 43 of AML; mother died at 85 of natural causes with history of uterine cancer, dementia, and anemia

History of Present Illness

- **27 months ago:** Donna first experienced pain in the upper back and rib area after a sneeze; this was attributed to a muscle strain, and Donna continued her workout regimen
- **24 months ago:** After her rib and back pain became unbearable and she had additional pain in her left leg, Donna visited her PCP again. The ordered X-ray revealed multiple rib fractures and a left femoral fracture. Her bloodwork revealed elevated creatinine (1.6 mg/dL), M-protein of 3.7 g/dL (IgG Lambda type), and serum free light chain of 247.6 mg/dL, resulting in an initial diagnosis of multiple myeloma. Bone marrow aspirate revealed 90% involvement, and diagnostic bone marrow using FISH reported standard cytogenetic risk
- **Initial therapy:** Donna received two cycles of doxorubicin liposomal, bortezomib, and dexamethasone, but M-protein and serum free light chain levels remained unchanged. Lenalidomide 10 mg was added in the third cycle to achieve deeper response. After 6 cycles, Donna achieved a partial response with decreased M-protein; her serum creatinine decreased to 1.0 mg/dL, and her bone pain improved. She continued on lenalidomide alone as maintenance therapy

Current Patient Assessment

- After 18 months of maintenance therapy, Donna now presents with new back pain and bilateral hip pain. MRI and CT-PET scan shows new vertebral fracture at L1 and new lesions in both femurs. FISH reports gain 1q21
- Laboratory values include:
  - WBC: 8.8 x 10^9/L; HB: 12.0 g/dL; Platelets: 332,000 per mcL
  - Creatinine increased to 1.8 mg/dL; eGFR 45 mL/min/1.73 m^2
  - Serum protein increased from 0.5 to 1.98 g/dL
  - Lambda Free light chain increased from 47.6 mg/dL to 137.8 mg/dL
  - M-protein: 1.98 g/dL
- ECOG PS 1

Treatment Goals and Plan

- Goal for Donna is to achieve a deep response and prolong progression-free survival, keeping her moderate renal impairment in mind
- Donna may benefit from a treatment that has consistent PFS results in patients with moderate renal dysfunction
- Dr Berenson discussed various triplet treatment options with Donna, and they decided to start her on SARCLISA in combination with carfilzomib and dexamethasone

With the approval of SARCLISA + Kd for use in adult patients with MM as early as first relapse, I have another option for patients who have received one prior line of therapy and are renally impaired, like Donna.[1] In my clinical experience, renal dysfunction in a patient with MM signifies an even greater need to treat quickly and to identify an option that doesn't require a dose modification, like SARCLISA. Key considerations for Donna's treatment plan are her increase in M-protein levels and serum free light chain, bone lesions, and worsening kidney disease. **– James R. Berenson, MD**

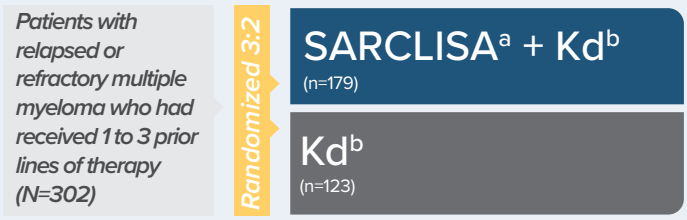
AML=acute myeloid leukemia; CT-PET=computed tomography-positron emission tomography; ECOG PS=Eastern Cooperative Oncology Group performance status; FISH=fluorescence in situ hybridization; HB=hemoglobin; M-protein=monoclonal protein; MRI=magnetic resonance imaging; PCP=primary care provider; WBC=white blood cells.

IKEMA was a randomized, phase 3 trial comparing SARCLISA + Kd vs Kd alone in patients with relapsed or refractory MM who had received 1 to 3 prior lines of therapy. The patients in IKEMA are reflective of the patients I treat in my practice, especially in terms of age, renal impairment, and cytogenetic risk.[1,8] In the trial, treatment was administered in 28-day cycles until disease progression or unacceptable toxicity; in the SARCLISA + Kd arm, patients were given SARCLISA 10 mg/kg weekly for the first cycle and then every 2 weeks thereafter, in combination with Kd.[1] – *James R. Berenson, MD*

About IKEMA

- IKEMA was a multicenter, multinational, randomized, open-label, phase 3 study of SARCLISA + Kd vs Kd alone in 302 patients with relapsed or refractory MM (Figure 2)[1,8]
- The primary endpoint was PFS*; key secondary endpoints were ORR, ≥VGPR, CR, OS, and MRD negativity[1,8]

Figure 2: Study Design for IKEMA[1,8]



Treatment was administered in 28-day cycles until disease progression or unacceptable toxicity.[1]

[a]SARCLISA 10 mg/kg was administered as an IV infusion weekly in the first cycle and every 2 weeks thereafter.[1]

[b]Carfilzomib was administered as an IV infusion during cycle 1 at a dose of 20 mg/m^2 on days 1 and 2, and at 56 mg/m^2 on days 8, 9, 15, and 16; during subsequent cycles, it was administered at 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16. Dexamethasone (IV on the days of SARCLISA and/or carfilzomib infusions, and orally on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle.[1]

SARCLISA + Kd Was Studied in a Broad and Diverse Population[1,8]

- Patients with poor prognostic factors at baseline† were included in IKEMA (Table 1)[1,8]

*PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. An interim analysis was conducted when 65% of the 159 PFS events (ie, 103 events) were observed.[1,8]

†Poor prognostic factors may include renal insufficiency, older age, high cytogenetic risk, and refractoriness to prior therapies.[4,5]

ASCT=autologous stem cell transplant; CR=complete response; eGFR=estimated glomerular filtration rate; IMWG=International Myeloma Working Group; IRC=independent response committee; ISS=International Staging System; IV=intravenous; MDRD=modification of diet in renal disease; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; y=years.

Table 1: Baseline Characteristics in IKEMA[1,8]

	SARCLISA + Kd (n=179)	Kd (n=123)
Age, y		
Median (range)	65 (37-86)	63 (33-90)
<65	49%	54%
65-74	41%	38%
≥75	9%	8%
Baseline eGFR (MDRD)		
<60 mL/min/1.73 m^2	24%	15%
ECOG PS		
0 or 1	94%	96%
2	6%	4%
ISS stage at study entry		
I	50%	58%
II	35%	25%
III	15%	16%
Cytogenetic risk at baseline		
High[a]	23%	25%
Standard	64%	63%
Unknown or missing	13%	11%
Prior lines of therapy[b]		
Median (range)	2 (1-4)	2 (1-4)
1	44%	45%
Prior therapies		
PI (bortezomib)	93% (91%)	85% (83%)
IMiD (lenalidomide)	76% (40%)	81% (48%)
Patient refractory to		
IMiD (lenalidomide)	44% (32%)	47% (34%)
PI	31%	36%
IMiD + PI	20%	22%
Previous ASCT		
Yes	65%	56%

[a]High-risk cytogenetic status is defined as the presence of del(17p) and/or t(4;14) and/or t(14;16). Chromosomal abnormality was considered positive if present in at least 30% of analyzed plasma cells, except for del(17p), where the threshold is at least 50%. Gain(1q21), present in 42% of patients, was also analyzed and was considered positive if there were at least 3 copies in at least 30% of analyzed plasma cells.[1,8]

[b]Inclusion criteria for the IKEMA study specified 1 to 3 prior lines of therapy; however, a small number of patients included in the study had received >3 prior lines of therapy (n=5/302, 1.7%).[8]

In IKEMA, the addition of SARCLISA to Kd provided a profound effect, reducing the risk of disease progression or death by 45% (HR=0.548, 95% CI: 0.37, 0.82; P=0.0032) vs Kd alone in patients with MM. At the time of the pre-planned interim analysis (median followup 20.7 months), patients who received Kd alone had a median PFS of 20.27 months, but the median PFS for SARCLISA + Kd had not been reached. The Kaplan-Meier curve shows a clear separation between the groups, which continued during the trial and reinforces use of SARCLISA + Kd long term.[1] It's important to note that PFS was consistent across almost all prespecified subgroups, including age, renal impairment, cytogenetic abnormality, or prior treatment, with the triplet regimen performing better than the doublet. In patients with renal impairment (eGFR <60 mL/min/1.73 m^2), like Donna, SARCLISA + Kd saw a 66% reduction in risk of disease progression vs Kd alone (HR=0.34; 95% CI: 0.13, 0.86; n=10/43 for SARCLISA + Kd vs 8/18 for Kd alone).[8] Patients in IKEMA had deep responses as well (73% ≥VGPR for SARCLISA + Kd vs 56% ≥VGPR for Kd alone).[1] I'm glad to have SARCLISA + Kd in my toolbox, as it's an option supported by strong clinical data. **– James R. Berenson, MD**

NCCN

RECOMMENDED

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend isatuximab-irfc (SARCLISA) for previously treated multiple myeloma[9]:

- in combination with pomalidomide and dexamethasone (Category 1, Preferred)
- in combination with carfilzomib and dexamethasone

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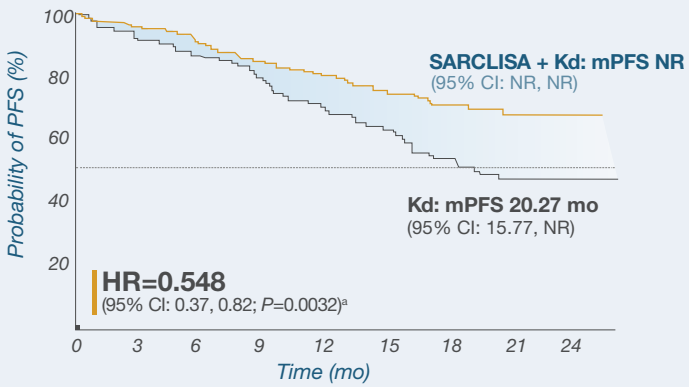
Figure 3: 45% Reduction in Risk of Progression or Death With SARCLISA + Kd vs Kd Alone[1]



No. at risk	0	3	6	9	12	15	18	21	24
SARCLISA + Kd	179	163	150	136	124	110	100	36	5
Kd	123	106	98	83	71	58	49	19	6

PFS results are based on a prespecified interim analysis, with a median follow-up time of 20.7 months. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria.

[a]Stratified by the number of previous lines of therapy (1 vs >1) and R-ISS stage (I or II vs III vs not classified) according to IRT.

In IKEMA, SARCLISA + Kd Demonstrated Superior PFS vs Kd Alone[1]

- At the median follow-up time of 20.7 months, the median PFS with SARCLISA + Kd is not yet reached (Figure 3)[1]
- The median duration of treatment was 80 weeks in the SARCLISA + Kd group vs 61 weeks for the Kd-only group[1]
- At the interim analysis cut-off date, 74% of patients in the SARCLISA + Kd arm had not progressed vs 59% of patients in the Kd arm[8]
- The PFS results seen in almost all subgroups were consistent with the ITT population* (see Figure 4)[8]
- In IKEMA, PFS results among patients with poor prognostic factors at baseline were consistent with the ITT population, including those with advanced age (≥65 years), renal impairment, high cytogenetic risk, and refractory status to lenalidomide* (highlighted in Figure 4)[5,8]
  - ***Study limitations:** prespecified subgroup analysis; subgroups were not powered to show differences between treatment arms

CI=confidence interval; HR=hazard ratio; IRT=interactive response technology; ITT=intent-to-treat; mo=months; mPFS=median progression-free survival; NCCN=National Comprehensive Cancer Network; NR=not reached; R-ISS=Revised International Staging System.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Neutropenia (cont)

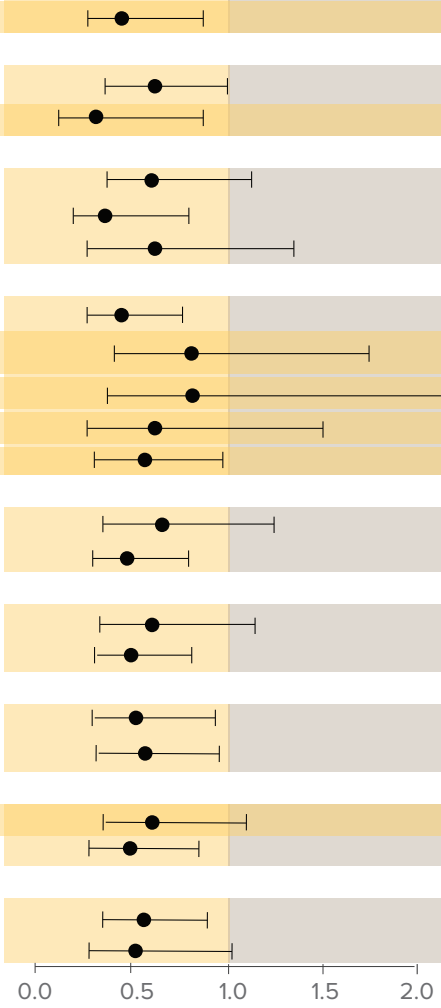
In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

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

Figure 4: Prespecified Subgroup Analysis of PFS for SARCLISA + Kd Compared With Kd Alone[8]

SUBGROUP	NO. OF EVENTS/TOTAL SARCLISA + Kd	NO. OF EVENTS/TOTAL Kd	HR (95% CI)
All patients	46/179	50/123	0.55 (0.37, 0.82)
Age			
<65 y	23/88	26/66	0.59 (0.34, 1.04)
≥65 y	23/91	24/57	0.50 (0.28, 0.89)
Baseline of eGFR (MDRD)			
≥60 mL/min/1.73 m²	30/122	36/93	0.61 (0.38, 0.99)
<60 mL/min/1.73 m²	10/43	8/18	0.34 (0.13, 0.86)
ISS stage at study entry			
I	20/89	22/71	0.64 (0.35, 1.16)
II	16/63	14/31	0.39 (0.19, 0.81)
III	10/26	14/20	0.60 (0.26, 1.34)
Cytogenetic abnormality			
Standard risk	27/114	34/77	0.45 (0.27, 0.75)
At least 1 high-risk cytogenetic abnormality[a]	16/42	12/31	0.81 (0.38, 1.72)
del(17p)	5/18	6/16	0.81 (0.25, 2.65)
t(4;14)	10/22	9/20	0.61 (0.25, 1.52)
gain(1q21)	25/75	26/52	0.55 (0.32, 0.95)
Prior lines of therapy			
1	18/80	17/55	0.65 (0.33, 1.26)
>1	28/99	33/68	0.48 (0.29, 0.80)
Prior PI in last line			
Yes	21/81	17/47	0.62 (0.33, 1.17)
No	25/98	33/76	0.50 (0.30, 0.84)
Prior IMiD in last line			
Yes	22/81	27/62	0.53 (0.30, 0.94)
No	24/98	23/61	0.55 (0.31, 0.97)
Refractory to lenadlidomide[b]			
Yes	22/57	23/42	0.61 (0.34, 1.10)
No	24/122	27/81	0.50 (0.29, 0.87)
Previous ASCT			
Yes	32/116	30/69	0.54 (0.33, 0.90)
No	14/63	20/54	0.52 (0.26, 1.03)



[a]High-risk cytogenetic status was defined as the presence of del(17p) and/or t(14;16). Chromosomal abnormality was considered positive if present in at least 30% of analyzed plasma cells, except for del(17p), where the threshold was at least 50%. [b]Lenalidomide-refractory subgroups were not prespecified.

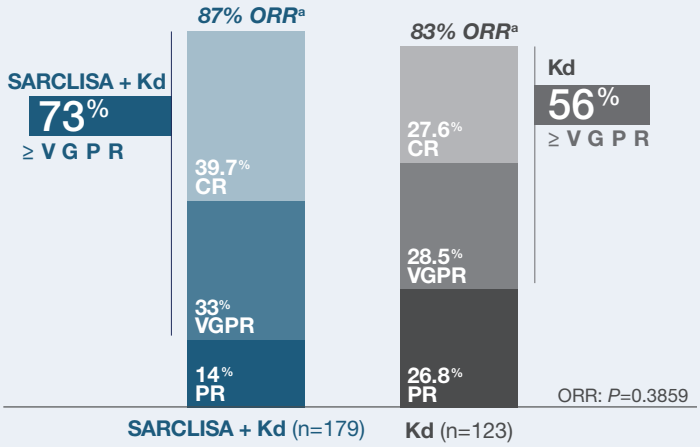
Study limitations: prespecified subgroup analysis; subgroups were not powered to show differences between treatment arms

Patients in the IKEMA Trial Achieved Deep Responses[1]*

- Response rates across treatment arms (key secondary endpoints) are shown in Figure 5
- As ORR did not reach statistical significance, CR, VGPR, and PR were not tested for significance[8]
  - ORR: SARCLISA + Kd, 87% (95% CI: 0.81, 0.91); Kd, 83% (95% CI: 0.75, 0.89). 95% CI estimated using the Clopper-Pearson method[1]
  - The median time to first response among responders was 1.08 months in the SARCLISA + Kd arm and 1.12 months in the Kd arm[8]

*A response of ≥VGPR.[8]
PR=partial response; sCR=stringent complete response.

Figure 5: Response Rates Across Treatment Arms in IKEMA[1]



[a]sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria. Results are based on a prespecified interim analysis with a median follow-up time of 20.7 months.[1]

In my evaluation of the safety profile from IKEMA, I paid close attention to cardiac events, knowing that these are included in the labeling for carfilzomib, and infusion-related reaction rates, given that SARCLISA is a mAb. I found that in the IKEMA study, the rates of infusion-related reactions (IRRs) and cardiac events were similar between the SARCLISA + Kd arm and the Kd arm.[1] Serious cardiac failure was seen in 4% of patients in the SARCLISA + Kd group and 3.3% of patients in the Kd group. IRRs occurred in 46% of patients in the SARCLISA + Kd arm, but only 0.6% of these reactions were above grade 2 severity. All IRRs were resolved on the same day in 74% of cases in the IKEMA trial, and only 0.6% of patients discontinued SARCLISA alone due to IRRs.[1] The nurses in my office, like Regina, provide patients with a thorough explanation of what to expect during the infusion process, and manage any reactions that may occur. In my experience, when patients are given the appropriate premedication at least 30 minutes before the SARCLISA infusion, IRRs may be managed. On days where both SARCLISA and carfilzomib are given, we administer dexamethasone first, then SARCLISA, and then carfilzomib to reduce potential IRRs.[1] **– James R. Berenson, MD**

Safety Profile for SARCLISA + Kd

- The safety profile for SARCLISA + Kd compared to Kd alone is shown in Table 2
- Serious adverse reactions occurred in 59% of patients receiving SARCLISA + Kd[1]
  - The most frequent serious adverse reactions in >5% of patients who received SARCLISA + Kd were pneumonia (25%) and upper respiratory tract infections (9%)
- Fatal adverse reactions occurred in 3.4% of patients receiving SARCLISA + Kd (those occurring in >1% of patients were pneumonia in 1.7% and cardiac failure in 1.1% of patients) vs 3.3% in the Kd arm[1,8]

Table 2: Adverse Reactions (≥10%) in Patients Receiving SARCLISA + Kd With a Difference Between Arms of ≥5% Compared With Kd Alone[1]

Adverse Reactions	SARCLISA + Kd (n=177)			Kd (n=122)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
General disorders and administration site conditions						
IRR[a]	46%	0.6%	0%	3.3%	0%	0%
Infections						
Upper respiratory tract infection[b]	67%	9%	0%	57%	7%	0%
Pneumonia[c]	36%	19%	3.4%	30%	15%	2.5%
Bronchitis[d]	24%	2.3%	0%	13%	0.8%	0%
Vascular disorders						
Hypertension[e]	37%	20%	0.6%	32%	18%	1.6%
Respiratory, thoracic, and mediastinal disorders						
Dyspnea[f]	29%	5%	0%	24%	0.8%	0%
Cough[g]	23%	0%	0%	15%	0%	0%
Gastrointestinal disorders						
Diarrhea	36%	2.8%	0%	29%	2.5%	0%
Vomiting	15%	1.1%	0%	9%	0.8%	0%
General disorders and administration site conditions						
Fatigue[h]	42%	5%	0%	32%	3.3%	0%

[a]IRR includes IRR, cytokine release syndrome, and hypersensitivity. [b]Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza-like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection. [c]Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, *Pneumocystis jirovecii* pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis. [d]Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis. [e]Hypertension includes hypertension, blood pressure increased, and hypertensive crisis. [f]Dyspnea includes dyspnea and dyspnea exertional. [g]Cough includes cough, productive cough, and allergic cough. [h]Fatigue includes fatigue and asthenia.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Neutropenia (cont)

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

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

Additional Safety Experience for SARCLISA + Kd

- Hematology laboratory abnormalities from IKEMA are shown in Table 3
- Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. In case of infection, appropriate standard therapy should be instituted. Antibiotics and antiviral prophylaxis can be considered during treatment[1]
- In IKEMA, cardiac failure*,† was reported in 7.3% of patients in the SARCLISA + Kd group (grade ≥3, 4%) and in 6.6% of patients in the Kd group (grade ≥3, 4.1%)[1]
  - Serious cardiac failure was observed in 4% of patients in the SARCLISA + Kd group and in 3.3% of patients in the Kd group

Table 3: Hematology Laboratory Abnormalities in Patients Receiving SARCLISA + Kd vs Kd Alone[1]

Laboratory parameter	SARCLISA + Kd (n=177)		
	All grades	Grade 3	Grade 4
Hemoglobin decreased	99%	22%	0%
Lymphocytes decreased	94%	52%	17%
Platelets decreased	94%	19%	11%
Neutrophils decreased	55%	18%	1.7%
Laboratory parameter	**Kd (n=122)**		
	All grades	Grade 3	Grade 4
Hemoglobin decreased	99%	20%	0%
Lymphocytes decreased	95%	43%	14%
Platelets decreased	88%	16%	8%
Neutrophils decreased	43%	7%	0.8%

The denominator used to calculate the percentage was based on the safety population.

- The addition of SARCLISA to Kd did not increase treatment discontinuations due to adverse reactions vs Kd alone[1,8]
- Permanent treatment discontinuation due to adverse reactions (grades 1 to 4) were 8% for SARCLISA + Kd compared with 14% for Kd alone[1,8]
  - The most frequent adverse reactions requiring permanent discontinuation were infections (2.8%, SARCLISA + Kd; 4.9%, Kd)
- Dosage interruptions due to an adverse reaction occurred in 33% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was IRR (30%)[1]

Infusion Related Reactions (IRRs)

- IRRs were observed in 46% and 38% of patients in the IKEMA and ICARIA-MM‡ trials, respectively[1]
  - In ICARIA-MM, all IRRs started during the first infusion of SARCLISA. In IKEMA, IRRs occurred on the infusion day in 99% of episodes, and 95% of patients receiving SARCLISA + Kd who experienced an IRR did so during the first cycle of treatment
  - All IRRs resolved on the same day in 98% of cases in the ICARIA-MM trial and in 74% of cases in the IKEMA trial
  - The most common symptoms (≥5%) of an IRR in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea
    - Anaphylactic reactions occurred in <1% of patients
- Serious IRRs, including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling[1]
- Dosage interruption of SARCLISA due to IRRs occurred in 30% and 28% of patients in the IKEMA and ICARIA-MM trials, respectively[1]
- SARCLISA alone was discontinued in 3% of patients in the ICARIA-MM trial and in 0.6% of patients in the IKEMA trial due to IRRs[1]

When observing the safety profile for SARCLISA + Kd, it's important to note that the addition of SARCLISA to Kd did not increase treatment discontinuations due to adverse reactions vs Kd alone (8% for SARCLISA + Kd vs 14% for Kd alone).[1,8] After starting Donna on SARCLISA + Kd, we monitored her hemoglobin and platelet levels, which are indicators of neutropenic or thrombocytopenic events; we also examined her renal status, given her history of impairment. Dosage interruptions due to ARs occurred in about 1/3 of patients who received SARCLISA—most frequently, these dose interruptions were due to IRRs.[1] We monitor patient vital signs closely during all infusions. If IRRs do occur, we determine the severity of the event, since we do not need to intervene for grade 1 IRRs. For grade 2-3 IRRs, we will interrupt the infusion and administer appropriate medications to mitigate the patient's symptoms. If symptoms have improved to grade ≤1 after 30 minutes, we begin infusion again at the initial rate. Although we haven't experienced any anaphylaxis or grade 4 IRRs in our practice, we would discontinue use of SARCLISA in those situations.[1] In my experience, reactions in patients receiving SARCLISA, either in combination with Kd or Pd, are often managed with premedication and some did not require discontinuation.

– Regina A. Swift, BSN, RN

*Cardiac failure included cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary edema.[1]

†See the current Prescribing Information for carfilzomib for more information.[1]

‡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 pomalidomide and dexamethasone (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. PFS was the primary endpoint; ORR and OS were key secondary endpoints. Median follow-up was 11.6 months.[1] For more information on ICARIA-MM, please see full prescribing information for SARCLISA.

SARCLISA is administered as 10 mg/kg, as an IV infusion in combination with Kd or Pd.[1] The key to reducing risk of IRRs is to premedicate patients 15-60 minutes prior to their SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone and stick to the titration. During a patient's first infusion in the absence of IRRs, we begin at a rate of 25 mL/h. If no IRRs occur during the first hour, then we increase the rate by 25 mL/h every 30 minutes.[1] I've found that if a patient can get through the initial infusion in the absence of IRRs, there's typically little to no difficulty with subsequent infusions. Because carfilzomib is also administered through IV, patients taking SARCLISA + Kd, like Donna, typically don't mind the administration method. Patients are often appreciative that the infusion time required for SARCLISA + Kd or Pd decreases to 75 minutes by the third infusion in the absence of IRRs,[1] allowing patients like Donna to spend less time in the infusion clinic. **– Regina A. Swift, BSN, RN**

With SARCLISA, Weekly Dosing Transitions to Every Other Week After the First Cycle[1]

- The recommended dose for SARCLISA is 10 mg/kg actual body weight, administered as an IV infusion in combination with Kd or Pd (Figure 6)[1]
  - On days where both SARCLISA and carfilzomib are administered, administer dexamethasone first, followed by SARCLISA infusion, then followed by carfilzomib infusion
  - For additional dosing instructions for combination agents administered with SARCLISA, please refer to the respective manufacturer's Prescribing Information
- Treatment is administered in 28-day cycles and is repeated until disease progression or unacceptable toxicity[1]

Figure 6: Dosing for SARCLISA[1]

- In the absence of IRRs, infusion time for SARCLISA decreases to 75 minutes after the second infusion (Table 4)[1]
  - There is a fixed infusion volume of 250 mL
  - Administer recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion. No post-infusion medications are required for SARCLISA
  - SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage IRRs if they occur
- For additional dosing instructions for combination agents administered with SARCLISA, refer to the study design descriptions in the SARCLISA Prescribing Information and the respective manufacturer's Prescribing Information

Table 4: Calculated Infusion Rates for SARCLISA[1]

Incremental escalation of the infusion rate should be considered only in the absence of IRRs

	Dilution volume	Initial rate	Absence of IRR	Rate increment	Maximum rate	Total time (if no rate adjustments)
First infusion	250 mL	25 mL/h	60 min	25 mL/h every 30 min	150 mL/h	**3 h 20 min**
Second infusion	250 mL	50 mL/h	30 min	50 mL/h for 30 min, then increase by 100 mL/h	200 mL/h	**1 h 53 min**
Subsequent infusions	250 mL	200 mL/h	--	--	200 mL/h	**75 min**

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 3.6%.

In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

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

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

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H_2 antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, 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. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

Neutropenia

SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

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

Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 3.6%.

In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In IKEMA, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCLISA-containing regimens and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with SARCLISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resection of the skin cancer.

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). The indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-Kd treatment in 63% of 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.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

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 that 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

In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets.

In combination with carfilzomib and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

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%]).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

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 accompanying full Prescribing Information.

References

1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Moreau P, Zamagni E, Mateos M-V. Treatment of patients with multiple myeloma progressing on frontline-therapy with lenalidomide. *Blood Cancer J*. 2019;9(4):38. doi:10.1038/s41408-019-0200-1. **3.** Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. *Leukemia*. 2020. doi:10.1038/s41375-020-01021-3. **4.** Jhaveri M, Romanus D, Raju A, et al. Real-world prescribing patterns in U.S. multiple myeloma (MM) patients refractory to lenalidomide in the front line. Poster presented at: 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark. **5.** Hájek R, Jarkovsky J, Maisnar V, et al. Real-world outcomes of multiple myeloma: retrospective analysis of the Czech Registry of Monoclonal Gammopathies. *Clin Lymphoma Myeloma Leuk*. 2018;18(6):e219-e240. **6.** Martin TG, Corzo K, Chiron M, et al. Therapeutic opportunities with pharmacological inhibition of CD38 with isatuximab. *Cells*. 2019;8(12):E1522. **7.** 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. **8.** Data on file. sanofi-aventis U.S. LLC. **9.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.7.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 28, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org.

Final Thoughts From Dr Berenson and Ms Swift

I believe that treating relapsed multiple myeloma is not necessarily about "more;" it's about being "more specific," which means finding an individualized treatment option. Tumor-, disease-, and patient-related factors should all be considered. SARCLISA, an anti-CD38 mAb that binds to a specific epitope on the surface of myeloma cells, works to enhance immune cell function while directly destroying cancer cells. With the approval of SARCLISA + Kd for use in adult patients with RRMM as early as first relapse, I have another option for patients who have received one prior line of therapy and are renally impaired, like Donna.[1] I'm glad to have SARCLISA + Kd in my toolbox, as it's an option supported by strong clinical data. **– James R. Berenson, MD**

When determining next steps in treatment at our clinic, Dr Berenson and I use an individualized approach. The triplet therapy of SARCLISA + Kd is an attractive treatment option for patients like Donna who are renally impaired. As a registered nurse, I also appreciate that there are no dose modifications recommended for patients with moderate-to-severe renal dysfunction.[1] In our practice, we inform patients about potential adverse events and educate them about what to expect during their infusion. Most reactions in patients receiving SARCLISA, either in combination with Kd or Pd, are often manageable through administration guidelines and monitoring. **– Regina A. Swift, BSN, RN**

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

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

Additional Resource: https://www.sarclisahcp.com/

This program was developed in conjunction with and sponsored by Sanofi Genzyme, based on interviews with James R. Berenson, MD and Regina A. Swift, BSN, RN.

Dr Berenson and Ms Swift each received compensation from Sanofi Genzyme for participation in this program.

SANOFI GENZYME

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