For your adult patients with relapsed or refractory multiple myeloma

FINAL ANALYSIS

~42 MONTHS

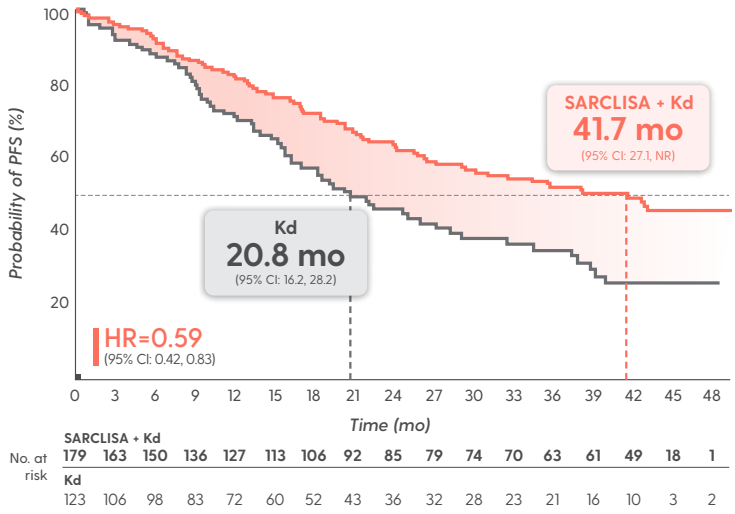
UNPRECEDENTED mPFS WITH SARCLISA + Kd[1-5]

LONGEST EVER REPORTED

in a phase 3 trial that included lenalidomide-refractory patients*

*Based on a review of published phase 3 trials that included lenalidomide-refractory patients with relapsed or refractory multiple myeloma. Interpret with caution, as various factors, including patient population, differ between trials.

SARCLISA + Kd doubled mPFS vs Kd alone at a median follow-up of 44 months[2]



PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using IMWG criteria. A preplanned interim analysis was conducted when 65% of 159 PFS events were observed. *P* value is not reported as this is a non-inferential analysis of the primary endpoint that was met at the time of the interim analysis.[1,6]

Superior PFS vs Kd at interim analysis (median follow-up of 20.7 months)[1]	**SARCLISA + Kd: mPFS NR** **Kd: mPFS 20.27 months[1]**	HR=0.548 (95% CI: 0.37, 0.82; *P*=0.0032)[1]

Final analysis: A prespecified final analysis was conducted when 159 PFS events were observed, with a median follow-up of 44 months.[2]

IMWG=International Myeloma Working Group; IRC=independent response committee; Kd=carfilzomib and dexamethasone; M-protein=monoclonal protein; mPFS=median progression-free survival; NR=not reached; PFS=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 2 prior therapies including lenalidomide and a proteasome inhibitor
- In combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy

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.

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

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

IKEMA Trial: SARCLISA + Carfilzomib and Dexamethasone (Kd)

Evaluated in 302 patients in a phase 3, multicenter, multinational, randomized, open-label study[1,6]

Patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy (N=302)

Randomized 3:2

- SARCLISA[a] + Kd[b] (n=179)
- Kd[b] (n=123)

PRIMARY ENDPOINT: PFS*

Key secondary endpoints: ORR, ≥VGPR, CR, MRD-, OS

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]

*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 159 PFS events (ie, 103 events) were observed. A prespecified final analysis was conducted when 159 PFS events were observed, with a median follow-up of 44 months.[1,2,6]

CR=complete response; IV=intravenous; MRD=minimal (or measurable) residual disease; MRD-=MRD negative/negativity; ORR=overall response rate; OS=overall survival; VGPR=very good partial response.

Important Safety Information (cont'd)

Infusion-Related Reactions (cont'd)

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%).

IKEMA Key Secondary Endpoints

Deep responses+ were seen in the IKEMA trial[2]

Secondary outcomes[1a]	SARCLISA + Kd (n=179)	Kd (n=123)
ORR	**87%**	84%
≥VGPR	**73%**	56%
CR	**44.1%**	28.5%
MRD- (ITT)	**33.5%**	15.4%

[a]sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria. Results are based on a prespecified final analysis with a median follow-up time of 44 months.[1,2]

Interim analysis (20.7 months median follow-up)[1,6]

- ***ORR:***
  - 86.6% (95% CI: 0.81, 0.91) with SARCLISA + Kd
  - 82.9% (95% CI: 0.75, 0.89) with Kd alone
  - *P*=0.3859; 95% CI estimated using the Clopper-Pearson method
- ***≥VGPR:*** 72.6% with SARCLISA + Kd vs 56.1% with Kd alone
- ***CR:*** 39.7% with SARCLISA + Kd vs 27.6% with Kd alone
- ***MRD-:*** 30% with SARCLISA + Kd (95% CI: 0.23, 0.37) vs 13% with Kd alone (95% CI: 0.08, 0.20)

Study limitations

As ORR did not reach statistical significance, ≥VGPR, MRD-, and CR were not tested for significance. According to the FDA, using MRD to assess clinical benefit of a multiple myeloma treatment should only be assessed in patients who achieve a CR or sCR. In the IKEMA trial, MRD was assessed in patients who achieved ≥VGPR. Additionally, there was an amount of missing data that did not meet the FDA's threshold for label inclusion. This analysis requires cautious interpretation and clinical significance of these data is unknown.

+A response of ≥VGPR.[6]

ITT=intent to treat; PR=partial response; sCR=stringent complete response.

Important Safety Information (cont'd)

Neutropenia (cont'd)

Monitor complete blood cell counts periodically during treatment. Consider the use of antibacterial 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 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 4.1%.

In ICARIA-MM, at a median follow-up time of 52 months, second primary malignancies occurred in 7% of patients in the Isa-Pd arm and in 2% of patients in the Pd arm.

In the ongoing IKEMA study, at a median follow-up time of 21 months, 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 (5% with SARCLISA-containing regimens and 2.6% with comparative regimens) and solid tumors other than skin cancer (3% with SARCLISA-containing regimens and 1.8% with comparative regimens). All patients with non-melanoma 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.

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

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

An Established Safety Profile

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%
Fatigue[b]	42%	5%	0%	32%	3.3%	0%
Infections						
Upper respiratory tract infection[c]	67%	9%	0%	57%	7%	0%
Pneumonia[d]	36%	19%	3.4%	30%	15%	2.5%
Bronchitis[e]	24%	2.3%	0%	13%	0.8%	0%
Vascular disorders						
Hypertension[f]	37%	20%	0.6%	32%	18%	1.6%
Respiratory, thoracic, and mediastinal disorders						
Dyspnea[g]	29%	5%	0%	24%	0.8%	0%
Cough[h]	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%

[a]IRR includes IRR, cytokine release syndrome, and hypersensitivity.
[b]Fatigue includes fatigue and asthenia.
[c]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.
[d]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.
[e]Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.
[f]Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.
[g]Dyspnea includes dyspnea and dyspnea exertional.
[h]Cough includes cough, productive cough, and allergic cough.

Serious adverse reactions

- 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[1,6]

Cardiac failure[1]*+

- In IKEMA, cardiac failure was reported in 7% of patients in the SARCLISA + Kd group (grade ≥3, 4%) and in 7% of patients in the Kd group (grade ≥3, 4.1%)
- Serious cardiac failure was observed in 4% of patients in the SARCLISA + Kd group and in 3.3% of patients in the Kd group

*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.

IRR=infusion-related reaction.

INTERIM ANALYSIS: 21 months median follow-up

Discontinuation Rates Did Not Increase With the Addition of SARCLISA to Kd

Permanent treatment discontinuation due to adverse reactions (grades 1 to 4)[1,6]

SARCLISA + Kd	Kd
8%	14%

- 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]

Hematology laboratory abnormalities in patients receiving SARCLISA + Kd vs Kd alone[1]

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

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

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. Antibacterial and antiviral prophylaxis can be considered during treatment.

Safety Update From the IKEMA Final Analysis[2]

	SARCLISA + Kd (n=177)	Kd (n=122)
Median treatment exposure	94 weeks	62 weeks
Serious adverse reactions	70.1%	59.8%
Fatal adverse reactions	5.6%	4.9%
Cardiac failure, grade ≥3 (any class[a]*)*	4.5%	4.1%
Permanent discontinuation due to adverse reactions (grades 1 to 4)	12.4%	18.0%

[a]Grouping using MedDRA SMQ cardiac failure narrow terms.

The safety profile at the longer follow-up remained consistent with the interim analysis, with the most frequent adverse reactions (all grades) in the SARCLISA + Kd group being IRRs (45.8%), diarrhea (39.5%), hypertension (37.9%), and upper respiratory tract infections (37.3%).

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

NCCN

CATEGORY 1 PREFERRED

National Comprehensive Cancer Network® (NCCN®) recommends isatuximab-irfc (SARCLISA) in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma as a Category 1 Preferred option in combination with carfilzomib and dexamethasone or with pomalidomide and dexamethasone[7]:

- ✓ For early relapses (1-3 prior therapies)*
- ✓ Option for patients refractory to either lenalidomide or bortezomib

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.
Recommendation for isatuximab-irfc (SARCLISA) in combination with carfilzomib and dexamethasone based on results of interim analysis.
*After 2 prior therapies including lenalidomide and a proteasome inhibitor for isatuximab-irfc in combination with pomalidomide and dexamethasone.
NCCN=National Comprehensive Cancer Network® (NCCN®).

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Important Safety Information (cont'd)

Laboratory Test Interference (cont'd)

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 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 accompanying full Prescribing Information.

References: 1. SARCLISA [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. **2.** Moreau P, Dimopoulos M-A, Mikhael J, et al; IKEMA study group. Updated progression-free survival and depth of response in IKEMA, a randomized phase 3 trial of isatuximab, carfilzomib and dexamethasone (Isa-Kd) vs Kd in relapsed multiple myeloma. Presented at: the 8th World Congress on Controversies in Multiple Myeloma (COMy); May 12-15, 2022; Paris, France. **3.** Hernández-Rivas J-A, Ríos-Tamayo R, Encinas C, Lahuerta J-J. The changing landscape of relapsed and/or refractory multiple myeloma (MM): fundamentals and controversies. *Biomarker Res*. 2022;10(1):1-23. **4.** Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. *Lancet Oncol*. 2022;23:65-76. **5.** Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol*. 2007;25(25):3892-3901. **6.** Data on file. sanofi-aventis U.S. LLC. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.3.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed December 19, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.

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