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

NOW APPROVED: SARCLISA + Kd

IKEMA Trial Summary

*Prescribe SARCLISA + Kd **as early as first relapse** for adult patients with relapsed or refractory multiple myeloma*[1]

Kd=carfilzomib and dexamethasone.

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.

SARCLISA is indicated, 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.

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.

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

IKEMA Trial: **SARCLISA + Carfilzomib and Dexamethasone (Kd)**

Evaluated in 302 patients in a phase 3, multicenter, multinational, randomized, open-label study[1,2]

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 negativity, OS

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

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

Patients with poor prognostic factors at baseline were included in IKEMA[1,2]

- **49%** *Older age (≥65 years)*
- **20%** *Impaired renal function*
- **24%** *High cytogenetic risk*

Overall, demographic and disease characteristics at baseline were similar between the 2 treatment groups. The median patient age was 64 years (range, 33-90); 9% of patients were aged ≥75 years. The median number of prior lines of therapy was 2 (range 1-4), with 44% of patients who received 1 prior line of therapy.[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 the 159 PFS events (ie, 103 events) were observed.[1,2]

CR=complete response; eGFR=estimated glomerular filtration rate; IMWG=International Myeloma Working Group; IRC=independent response committee; IV=intravenous; M-protein=monoclonal protein; mPFS=median progression-free survival; MRD=minimal (or measured) residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; VGPR=very good partial response.

Important Safety Information (cont'd)

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.

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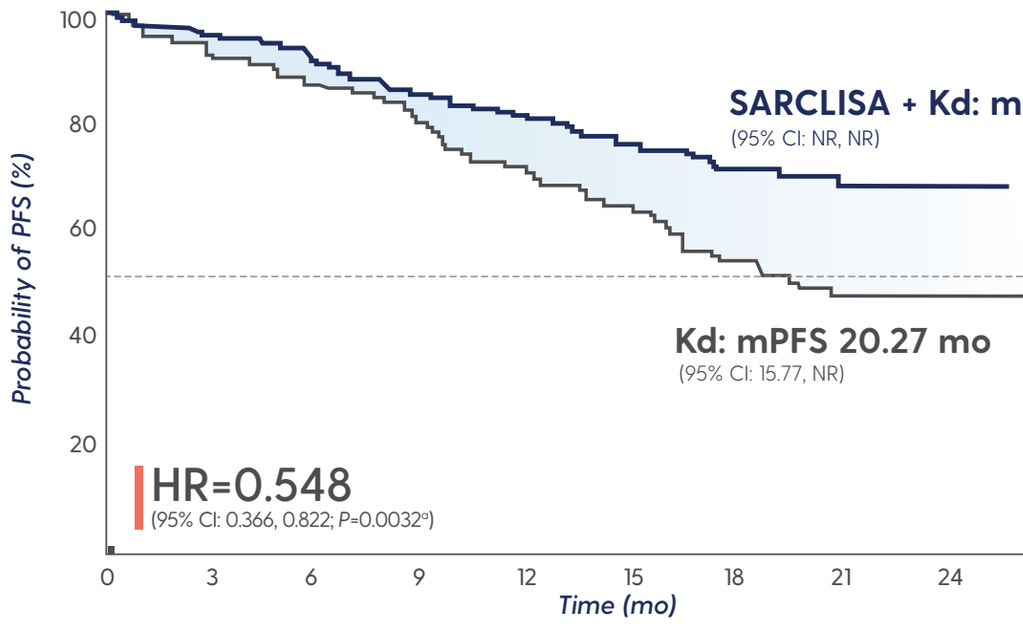
IKEMA Efficacy

SARCLISA + Kd demonstrated superior PFS, with a mPFS that is not yet reached (NR)[1]



45% reduction in risk of progression or death

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.[1]

[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.

Key secondary outcomes[1]

As ORR did not reach statistical significance, CR and VGPR were not tested for significance[2]

Secondary outcomes[1,a]	SARCLISA + Kd (n=179)	Kd (n=123)
ORR (*P*=0.3859)	87%	83%
95% CI[b]	(0.81, 0.91)	(0.75, 0.89)
≥VGPR	73%	56%
CR	39.7%	27.6%

[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]

[b]Estimated using the Clopper-Pearson method.[1]

Most common adverse reactions[1,2]

The most common adverse reactions (≥20%) were upper respiratory tract infection (67%, SARCLISA + Kd; 57%, Kd), IRRs (46%, SARCLISA + Kd; 3.3%, Kd), fatigue (42%, SARCLISA + Kd; 32%, Kd), hypertension (37%, SARCLISA + Kd; 32%, Kd), diarrhea (36%, SARCLISA + Kd; 29%, Kd), pneumonia (36%, SARCLISA + Kd; 30%, Kd), dyspnea (29%, SARCLISA + Kd; 24%, Kd), insomnia (24%, SARCLISA + Kd; 23%, Kd), bronchitis (24%, SARCLISA + Kd; 13%, Kd), cough (23%, SARCLISA + Kd; 15%, Kd), and back pain (22%, SARCLISA + Kd; 21%, Kd).

IRR=infusion-related reaction; IRT=interactive response technology; ITT=intent to treat; PR=partial response; R-ISS=Revised International Staging System; sCR=stringent complete response.

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TO LEARN MORE ABOUT SARCLISA + Kd FOR ADULT PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA AS EARLY AS FIRST RELAPSE,[1] contact your Sanofi Genzyme representative or visit sarclisahcp.com/contact-a-rep

Important Safety Information (cont'd)

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.

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. Data on file. sanofi-aventis U.S. LLC.

SANOFI GENZYME

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