RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Sarclisa®
Generic Name	isatuximab-irfc
Drug Manufacturer	SANOFI AVENTIS US

New Drug Approval

FDA Approval Date: March 2, 2020
Review Designation: Orphan
Type of Review: Biologics License Application 761113

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple myeloma (MM) is typically characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The plasma cells proliferate in the bone marrow and can result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures.

MM is a relatively uncommon cancer accounting for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies. It is more common in men than women, and more common among individuals of African American descent. Data from the US Surveillance, Epidemiology, and End Results (SEER) registry estimate 32,000 new cases of MM and 13,000 deaths from MM annually in the US. This correlates with an annual incidence of approximately 7 per 100,000 men and women per year. Worldwide, there are approximately 160,000 cases and 106,000 deaths per year attributed to MM. [2]

Almost all patients with MM who survive initial treatment will eventually relapse, experiencing relapsing-remitting MM (RRMM). Treatment options for patients with RRMM include hematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include risk stratification (i.e. high- or standard-risk disease), prior treatments used, and the duration of response to these treatments. Medications used include Velcade (bortezomib), Kyprolis (carfilzomib), Revlimid (lenalidomide), Pomalyst (pomalidomide), Darzalex (daratumumab), Ninlaro (ixazomib), Empliciti (elotuzumab), Farydak (panobinostat), and Doxil (doxorubicin liposome). Xpovio (selinexor) is also available for patients who have had at least four prior therapies.

In the triple-drug regimens that are increasingly the norm for treating MM, patients typically receive one or two active agents in combination with the steroid dexamethasone and are treated until disease progression, after which another dexamethasone-containing regimen is given.

Efficacy

The approval of Sarclisa is based on results of the Phase 3 ICARIA-MM (NCT 02990338) trial, which examined the use of Sarclisa with Pomalyst (pomalidomide) and dexamethasone compared to Pomalyst with dexamethasone (Pd). ICARIA-MM is an open-label, multicenter Phase 3 clinical study that included 307 patients with relapsed/refractory multiple myeloma who received ≥2 prior lines of treatment, including Revlimid and a proteasome inhibitor such as Velcade, Kyprolis, or Ninlaro. The median patient age was 67 years. In addition, patients had received a median of 3 (range, 2-11) prior lines of therapy.

Primary outcome measure was progression free survival (PFS). Among many secondary outcome measures, the following were included: overall response rate (ORR), overall survival (OS), time to progression (TPP), duration of

response (DOR), pharmacokinetic data, number of participants with anti-drug antibodies, and time to first response. ORR was divided into stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). In MM, a CR is when a patient has achieved a negative immunofixation on the serum and urine, disappearance of soft tissue plasmacytomas and achieves less than or equal to 5% plasma cells in the bone marrow. An sCR includes all CR criteria, plus the patient is required to have a normal free light chain ratio in the serum and absence of clonal cells in the bone marrow, which determined by either immunofluorescence or immunohistochemistry.

Efficacy of Sarclisa from the ICARIA-MM Clinical Study		
Endpoint	**Sarclisa + Pomalyst + Dexamethasone N=154**	**Pomalyst + Dexamethasone N=153**
Progression Free Survival		
Median (months) (95% CI)	11.53 (8.94–13.9)	6.47 (4.47–8.28)
Hazard ratio (95% CI)	0.596 (0.44–0.81)	
p-value	0.0010	
Overall Response Rate Responders (sCR+CR+VGPR+PR) n (%) (95% CI)	93 (60.4) (52.2–68.2)	54 (35.3) (27.8–43.3)
p-value	<0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n (%)	7 (4.5)	3(2)
Very Good Partial Response (VGPR) n (%)	42 (27.3)	10 (6.5)
Partial Response (PR) n (%)	44 (28.6)	41 (26.8)

At a median follow-up of 11.6 months, the median PFS was 11.53 months with the Sarclisa regimen compared with 6.47 months with Pd alone. OS data were not yet mature at the time of analysis. The median OS was not reached in either arm. The 1-year OS rate was 72% with the Sarclisa arm compared with 63% with Pd-alone arm.

PFS was seen across multiple patient subgroups, including patients with high cytogenetic risk, patients refractory to Revlimid, patients refractory to a proteasome inhibitor, and patients refractory to Revlimid and a proteasome inhibitor.

The ORR in the Sarclisa arm showed a stringent complete response (sCR) rate of 4.5%, a very good partial response rate (VGPR) of 27.3%, and a partial response (PR) rate of 28.6%. This compares to the non-Sarclisa arm, which showed response rates of 2.0%, 6.5%, and 26.8%, respectively. In addition, the median time to first response was 35 days with the Sarclisa arm compared to 58 days with Pomalyst-alone arm. The median duration of treatment was 41 weeks (range, 1.3–76.7) in the Sarclisa arm compared to 24.0 weeks (range, 1.0–73.7) in the Pomalyst-alone arm. In the Sarclisa arm, 56.5% of patients discontinued treatment compared to 74.5% of patients in the Pomalyst-alone arm. Progressive disease was the primary reason for discontinuation in both arms.

Safety

ADVERSE EVENTS

NEW DRUG APPROVAL

The most common adverse reactions (in ⩾20% of patients) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea. The most common hematology laboratory abnormalities (in ⩾80% of patients) were anemia, neutropenia, lymphopenia, and thrombocytopenia

WARNINGS & PRECAUTIONS

- Infusion-Related Reactions
  - Related Reactions: Interrupt SARCLISA and manage medically. Permanently discontinue for grade ≥3 reactions.
- Neutropenia
  - Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. SARCLISA dose delays and the use of colony-stimulating factor may be required to allow improvement of neutrophil count.
- Second Primary Malignancies (SPM)
  - Monitor patients for the development of second primary malignancies, as per IMWG guidelines.
- Laboratory Test Interference
  - Interference with Serological Testing (Indirect Antiglobulin Test): Type and screen patients prior to starting treatment. Inform blood banks that a patient has received SARCLISA.
  - Interference with Serum Protein Electrophoresis and Immunofixation Tests: SARCLISA may interfere with the assays used to monitor M-protein, which may impact the determination of complete response.
- Embryo-Fetal Toxicity
  - SARCLISA may cause fetal immune cell depletion and decreased bone density. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child.

CONTRAINDICATIONS

Patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients

Clinical Pharmacology

MECHANISMS OF ACTION

Isatuximab-irfc is an IgG1-derived monoclonal antibody that binds to CD38 expressed on the surface of hematopoietic and tumor cells, including multiple myeloma cells. Isatuximab-irfc induces apoptosis of tumor cells and activation of immune effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab-irfc inhibits the ADP-ribosyl cyclase activity of CD38. Isatuximab-irfc can activate natural killer (NK) cells in the absence of CD38-positive target tumor cells and suppresses CD38-positive T-regulatory cells. The combination of isatuximab-irfc and pomalidomide enhanced ADCC activity and direct tumor cell killing compared to that of isatuximab-irfc alone in vitro, and enhanced antitumor activity compared to the activity of isatuximab-irfc or pomalidomide alone in a human multiple myeloma xenograft model.

Dose & Administration

ADULTS

Given in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Cycle 1: 10 mg/kg on days 1, 8, 15, and 22 of a 28-day cycle (in combination with pomalidomide and dexamethasone).

Cycle 2 and beyond: 10 mg/kg on days 1 and 15 of a 28-day cycle (in combination with pomalidomide and dexamethasone), continue until disease progression or unacceptable toxicity (Attal 2019).

Missed dose: If a planned isatuximab dose is missed, administer the dose as soon as possible and then adjust the treatment schedule accordingly, maintaining the treatment interval.

Premedications: Administer 15 to 60 minutes prior to initiating isatuximab infusion to reduce the risk of infusion reaction:

- Dexamethasone 40 mg IV or oral (20 mg IV or oral in patients ≥75 years of age); this dose corresponds to the dose used as part of the backbone combination treatment; administer only once on days isatuximab is administered.
- Acetaminophen 650 mg to 1 g oral (or equivalent).
- An H_2 antagonist.
- Diphenhydramine 25 to 50 mg IV or oral (or equivalent); for at least the first 4 infusions, the IV route is preferred.

PEDIATRICS

Safety and effectiveness have not established in pediatric patients.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is necessary.

HEPATIC IMPAIRMENT

No dosage adjustment is necessary.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 100 mg/5 mL (20 mg/mL) solution in single-dose vial
- 500 mg/25 mL (20 mg/mL) solution in single-dose vial