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NCCN Guidelines Panel: Multiple Myeloma

Dear NCCN Guidelines Multiple Myeloma Panel:

On behalf of Sanofi Genzyme, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data for inclusion of isatuximab (Sarclisa®) as a treatment option for management of patients with relapsed/refractory multiple myeloma (RRMM).

Specific Changes:
Within the NCCN Multiple Myeloma Guidelines (Version 2.2020), recommend isatuximab as a treatment option for eligible adult patients with relapsed/refractory multiple myeloma.

FDA clearance:
Isatuximab is an approved compound developed by Sanofi Genzyme for the treatment of patients with RRMM. Isatuximab was approved by the FDA on March 2, 2020.

Rationale:
Phase 3 study[1]
ICARIA was a randomized, open-label, multicenter, phase 3 trial that compared isatuximab (Isa) combined with pomalidomide (P) and low-dose dexamethasone (d) versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). The primary objective of this trial was progression free survival (PFS). Patients included in this study received ≥2 prior lines, including lenalidomide (len) and a proteasome inhibitor (PI) and were refractory to last therapy. Patients in the Isa-Pd arm received isatuximab 10 mg/kg IV weekly for the first 4 weeks, then every 2 weeks. Patients in both arms received pomalidomide and dexamethasone (4mg PO days 1-21; 40mg [20mg if >75 years] PO or IV weekly) every 28 days until disease progression or unacceptable toxicity.

A total of 307 patients (154 Isa-Pd, 153 Pd) were randomized and analyzed. The median age was 67 (36-86) years and median number of prior lines of therapy was 3. In the ITT population, 56.8% of patients had renal impairment (eGFR <60 mL/min/1.73 m^2 or worse); 19.5% had high-risk cytogenetics at baseline.

At a median follow-up of 11.6 months, the median PFS was 11.53 months in the Isa-Pd arm versus 6.47 months in the Pd arm [HR 0.596 (95% CI 0.436-0.814), P=0.001]. Overall response rate (ORR) was 60.4% in the Isa-Pd arm versus 35.3% in the Pd arm, P<0.0001. Very good partial response (VGPR) rate or better was 31.8% in the Isa-Pd arm versus 8.5% in the Pd arm, and minimal residual disease (MRD) negativity (NGS, 10-5) was seen in 5.2% Isa-Pd patients vs 0% Pd patients. Median treatment duration was 41 weeks in the Isa-Pd arm versus 24 weeks in the Pd arm. The median Isa infusion duration was 3.3 hours at first infusion and 2.8 hours at subsequent infusions.

Grade ≥3 treatment emergent adverse events (TEAEs) were observed in 86.8% Isa-Pd patients versus 70.5% Pd patients. A total of 7.2% Isa-Pd patients and 12.8% Pd patients discontinued due to TEAEs; the rate of deaths due to TEAEs was 7.9% in the Isa-Pd arm and 9.4% in the Pd arm. Infusion reactions

(all grade) were reported in 38.2% (2.6% grade 3-4) Isa-Pd patients. The majority of infusion reactions occurred during first infusion and there were no delayed reactions. The rates of anemia, thrombocytopenia, and neutropenia (all grade) were similar in both arms. Grade 4 neutropenia was more frequent in the Isa-Pd arm (60.5%) vs. Pd arm (31.3%).

Phase 1 study[2]
Usmani et al. conducted a phase 1b, open label, multicenter study to assess the feasibility and safety of the infusion rates of isatuximab in combination with pomalidomide and dexamethasone (Pd) in patients with refractory/relapsed multiple myeloma. Patients received 10mg/kg of isatuximab at a fixed infusion volume of 250mL with standard doses of Pd. The first infusion was initiated at 25mL/h and slowly increased to 150mL if patients did not experience any infusion related reactions. The second infusion was initiated at 50mL/h and slowly increased to 300mL if patients did not experience any reactions. Remaining infusion reactions were initiated at a fixed rate of 200mL/h.

There were 47 patients initially enrolled in this study and about 30 patients remained on treatment at the data cut off point. About 45 patients started at least 2 cycles and 31 patients started at least 4. The average duration of exposure was 18.1 weeks. There were no grade 3/4 adverse events or treatment discontinuations due to infusion reactions. All the infusion reactions reported were grade 2 and occurred during the first infusion and were corrected with dose interruption or medications. There were no delayed infusion reactions reported throughout the duration of this process. The average time of the second infusion (1.85h) was almost that of the fist infusion (3.7h). The average duration of subsequent infusions was about 1.35h.

The following resources are submitted to assist the committee in their review:

1. Attal M, Richardson PG, Rajkumar SV, et al. 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. Early access.
2. Usmani S. Phase 1b study of feasibility/safety of isatuximab short duration fixed volume infusion in combination with pomalidomide and dexamethasone for relapsed/refractory multiple myeloma. Presented at: EHA 2019; Poster 1390.
3. Sarclisa [package insert]. Bridgewater, NJ: Sanofi Genzyme; 2020.

We appreciate the opportunity to provide this information for consideration by the NCCN Multiple Myeloma Panel. Thank you for your time and consideration of this request.

Sincerely,

Marian Ibrahim, PharmD
Manager, Oncology Medical Information
Sanofi Genzyme

Enclosures: Copies of referenced primary literature