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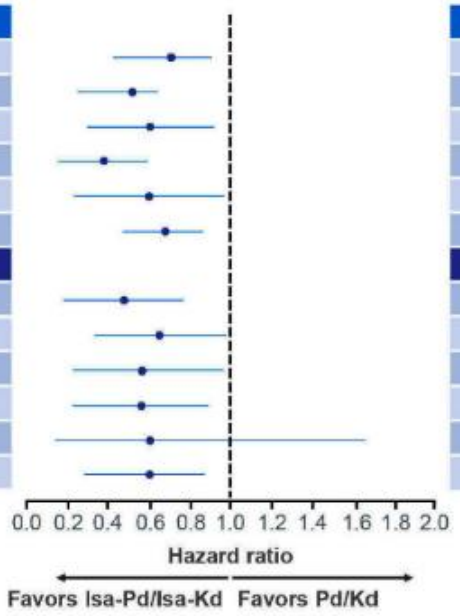
Positive Quality Intervention: Isatuximab-irfc (Sarclisa®) Regimens in 1q21 gain/amplification Relapsed/ Refractory Multiple Myeloma

Description: The purpose of this PQI is to discuss the potential activity isatuximab-irfc (Sarclisa®)-based regimens have on patients with 1q21 gain or amplification (1q21+) relapsed, refractory multiple myeloma (MM) with or without other high-risk features.

Background: Gain/amplification of 1q21 (1q21+) is a cytogenetic abnormality that may occur in both newly diagnosed and relapsed/refractory MM. It may occur alone or in combination with other cytogenetic abnormalities and is used for prognostic counseling, selection, and sequencing of therapy.[1,2] 1q21+ is detected in approximately 40% or more of newly diagnosed MM patients and 50-80% of those with relapsed/refractory MM. This is associated with worse outcomes, especially when it co-exists with other high-risk chromosomal abnormalities.[3] 1q21 gain is defined as 3 copies of 1q21 and amplification is defined as ≥ 4 copies and is detected by FISH.[1] For relapsed/refractory multiple myeloma after 1-3 prior therapies in patients who are refractory to either bortezomib or lenalidomide, isatuximab in combination with carfilzomib and dexamethasone (IsaKd) is an NCCN category 1 preferred treatment option based on the Phase 3 results in the IKEMA study.[3,4] Further, the final IKEMA subgroup analysis of high-risk patients with 1q21+ R/R MM exhibit a median progression free survival (mPFS) benefit: IsaKd mPFS was not reached versus 16.2 months (HR=0.57 (0.33-0.98) in patients who were treated with Kd alone.[1] For patients who have received 2 prior therapies, including lenalidomide and a PI, isatuximab in combination with pomalidomide and dexamethasone is an NCCN Category 1 preferred treatment option based on results from the Phase 3 ICARIA-MM trial.[1] Further subgroup analysis of high-risk patients with 1q21+ exhibits a median progression free survival (9.5 months versus 3.8 months) and median overall survival benefit (21.3 months versus 13.9 months).[3] Refer to the chart below for a forest plot from both trials for all subgroups related to 1q21+.[1] 1q21+ is an emerging space and data continues to evolve.

Progression Free Survival

1q21+ subgroup	Event rate (n/N)		Median (mo)		Hazard ratio (95% CI)
ICARIA-MM	Isa-Pd	Pd	Isa-Pd	Pd	ICARIA-MM
Standard risk	50/103	48/78	11.6	7.4	0.62 (0.42–0.93)
1q21+	41/76	37/52	9.5	3.8	0.40 (0.25–0.63)
Isolated 1q21+	32/56	20/29	11.2	4.6	0.50 (0.28–0.88)
Gain(1q21)	22/49	23/31	13.3	4.3	0.32 (0.17–0.59)
Amp(1q21)	19/27	14/21	8.9	2.3	0.49 (0.24–0.99)
All patients	73/154	89/153	11.5	6.5	0.60 (0.44–0.81)
IKEMA	Isa-Kd	Kd	Isa-Kd	Kd	IKEMA
Standard risk	14/65	20/43	NC	20.3	0.40 (0.20–0.79)
1q21+	26/75	26/52	NR	16.2	0.57 (0.33–0.98)
Isolated 1q21+	13/47	15/31	NC	16.2	0.46 (0.22–0.97)
Gain(1q21)	12/43	19/37	NC	18.2	0.46 (0.22–0.94)
Amp(1q21)	14/32	7/15	18.8	13.2	0.69 (0.28–1.71)
All patients	48/179	55/123	NC	19.2	0.53 (0.32–0.89)*



PQI Process: Consider isatuximab-based regimens for patients with Multiple Myeloma if

- Adult patients with relapsed or refractory multiple myeloma
- Received 1-3 prior lines of therapy (*Some patients may be eligible for 1st line therapy with isatuximab-based quadruplet therapy – clinical trials ongoing*)
- Gain or amplification of 1q21 with or without other high-risk cytogenetic abnormalities
- NOT refractory to previous treatment with an anti-CD38 monoclonal antibody
- Consider patient functional status, disease risk, comorbid conditions, reimbursement considerations, and patient preferences when evaluating treatment selections
- Prophylactic therapy recommendations for all patients receiving isatuximab
    - Assess and prescribe prophylactic treatment for bacterial, viral, and fungal infections
    - Prescribe prophylactic antiemetic therapy for the prevention of acute and delayed nausea and vomiting based on the emetogenic risk of the chemotherapy regimen - Refer to Chemotherapy-Induced Nausea and Vomiting PQI
    - Assess risk, monitor, and administer prophylaxis as indicated for deep venous thrombosis or pulmonary embolism as these may occur with therapy
- Dosing Guideline Summary – See Isatuximab-irfc (Sarclisa®) In Patients with Relapsed/Refractory Multiple Myeloma PQI

Patient-Centered Activities:

- Discuss risk of infusion reactions and diarrhea management:
    - See Isatuximab-irfc (Sarclisa®) In Patients with Relapsed/Refractory Multiple Myeloma PQI, Oncolytic Induced Diarrhea PQI, and OCE Supplemental Sheet
    - Advise patients to immediately report symptoms of infusion-related reactions and monitor vital signs frequently during infusion
- Review antiemetic therapy, both scheduled and as needed for breakthrough nausea and vomiting based on the chemotherapy regimen administered – See OCE Supplemental Sheet for Nausea & Vomiting
- Review key features of 1q21+ and isatuximab-irfc (Sarclisa®) based combination activity in this setting
- Ensure female patients of childbearing age avoid getting pregnant while on therapy and for at least 5 months after the last dose of isatuximab-irfc (Sarclisa®)
- Monitoring
    - Complete blood count with differential (CBC w/diff) and Complete Metabolic Panel (CMP)
    - Blood pressure (especially when in combination with carfilzomib)
    - Symptoms of low-grade fever, chills, sweating, sore throat, cough/shortness of breath
    - Development of secondary malignancies (skin cancers and other solid tumors)
- Patient Assistance: NCODA Financial Assistance Tool and Patient Treatment Calendar

References:

1. NCCN Guidelines: Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.
2. Burroughs Garcia J, Eufemiese RA, Storti P, et al. Role of 1q21 in Multiple Myeloma: From Pathogenesis to Possible Therapeutic Targets. Cells. 2021;10(6):1360. doi:https://doi.org/10.3390/cells10061360
3. Martin T, Richardson PG, Facon T, et al. Primary outcomes by 1q21+ status for isatuximab-treated patients with relapsed/refractory multiple myeloma: subgroup analyses from ICARIA-MM and IKEMA. Haematologica. 2022;107(10):2485-2491. doi:https://doi.org/10.3324/haematol.2022.280660
4. Sarclisa®(isatuximab-irfc) Package Insert.