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Positive Quality Intervention: Elranatamab (Elrexfio®) for the treatment of Relapsed/Refractory Multiple Myeloma

Description:
The purpose of this PQI is to discuss clinical considerations around using elranatamab (Elrexfio®) to optimize the outcomes for patients with treatment of relapsed/refractory multiple myeloma (RRMM).

Background: Elranatamab-bcmm (Elrexfio™) is a bispecific BCMA-directed CD3 T-cell engager approved for adults with relapsed or refractory multiple myeloma (RRMM) after at least four prior therapies including a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1] In the MagnetisMM-3 trial[2], RRMM patients received weekly elranatamab following two initial priming doses. Among 123 BCMA-naive patients, the overall response rate (ORR) was 61%, with 35% achieving a complete response or better. Fifty responders switched to bi-weekly dosing, and forty maintained or improved their response for at least six months. With a median follow-up of 14.7 months, the median duration of response (mDOR), progression-free survival (PFS), and overall survival (OS) were not reached at time of original publication. Common adverse events included infections (70%), cytokine release syndrome (58%), anemia (49%), and neutropenia (49%), with bi-weekly dosing reducing grade 3/4 adverse events from 59% to 47%.[2]

After a median follow-up of 33.9 months, 2/123 (16%) patients remained on therapy. Fifty-eight patients switched to bi-weekly dosing, and among the 43 responders, 28 transitioned to a four-week dosing schedule. The overall response rate (ORR) was 61%, with about 90% achieving MRD negativity. Median progression-free survival (PFS) was 17.2 months, and median overall survival (OS) was 24.6 months. Of those on monthly dosing, 93% maintained their response for at least six months, including 88% with a complete response or better. No new safety concerns emerged, and side effects were generally similar or less frequent in the monthly dosing group, with grade 3/4 infections decreasing from 18% to 11%.[3] This ultimately suggests that a four-week dosing schedule may improve safety without impacting efficacy.

PQI Process:[1, 2, 4]

REMS
Elranatamab is only available via REMS involving physicians, nurses, and pharmacists at the clinical facility

- Goal of the elranatamab REMS program is to mitigate and prevent CRS and ICANS[5]
- Elranatamab REMS consists of the following steps:

1. Review the Prescribing Information, Prescriber Training Program, and Adverse Reaction Management Guide.	4. Before starting treatment (initial dose increase), fill out the Patient Wallet Card and give it to the patient.
2. Complete and submit the Knowledge Assessment to REMS.	5. Always report severe CRS and neurologic toxicity events, including ICANS, to the REMS.
3. Enroll in the REMS by completing and submitting the Prescriber Enrollment Form to the REMS.	Prescribers cannot act as Authorized Representatives for elranatamab. Pharmacy and Healthcare Setting certification must be completed by a designated Authorized Representative.

Preparing for Administration

- Before medication initiation, conduct baseline labs including CBC, quantitative Immunoglobulins, FISH, and bone marrow biopsy
    - Maintaining adequate hydration and premedicate 1 hour before the first three doses with acetaminophen (650 mg), diphenhydramine (25 mg), and dexamethasone PO/IV (20 mg), or any equivalent, is required before each step-up dose of elranatamab
    - For CRS management (outlined below), ensure tocilizumab, dexamethasone, and methylprednisolone product availability

- Consider hospitalization for two ramp-up doses based on CRS risk; prior to hospitalization, patient education about the inpatient stay as well as authorization confirmation for subsequent outpatient care should be completed
- Recommendations for **antimicrobial prophylaxis and infection prevention**.[5]
    - **Bacterial**: Prophylaxis includes levofloxacin/ciprofloxacin/cefpodoxime/cefdinir. Start when ANC ≤ 0.5 K/mcL or ANC < 1.0 K/mcL is expected to last ≥ 7 days. Continue until ANC > 0.5 K/mcL for 3 consecutive days without growth
    - **Fungal**: Prophylaxis includes fluconazole or Echinocandin for low-risk patients; use Posaconazole, Voriconazole, Isavuconazole, or an echinocandin for high-risk patients. Start when ANC < 0.5 K/mcL. Continue until ANC > 0.5 K/mcL
    - **HSV/VZV**: Start valacyclovir or acyclovir with treatment. Discontinuation is indefinite irrespective of vaccination status
    - **PJP:** Start PJP prophylaxis with elranatamab initiation with either TMP-SMZ, Dapsone, or Atovaquone, and continue while on treatment or until CD4>200
    - **Neutropenia:** Filgrastim, Pegfilgrastim considered in patients with grade 3/4 neutropenia; avoid during periods of highest CRS risk
    - **Hypogammaglobulinemia:** During 2nd cycle of treatment, start IVIG 400 mg/kg once every 4 weeks until IgG > 400 mg/dL, check IgG levels monthly if patients are on IVIG

Dosing and Adverse Effects

	Week 1: Step Up doses		**Week 2: Treatment**	**Week 3 onwards: Treatments**	**Biweekly (Every 2 Weeks)**
Dosing Calendar Elranatamab (Elrexfio®)	Day 1	Day 4	Day 8	Once weekly from day 8* *Patients on a minimum of 24 weeks of Elranatamab-bcmm with partial or better responses for at least two months may transition to bi-weekly dosing	Week 25 and every 2 weeks
	12 mg	*32 mg*	*76 mg*	*76 mg weekly*	*76 mg weekly*
	0.3 mL SQ	*0.8 mL SQ*	*1.9 mL SQ*	*1.9 mL SQ weekly*	*1.9 mL SQ weekly*

- Single-use vial stored in fridge at 2˚C - 8˚C, should be at room temperature 15˚C - 30˚C before administration; BUD of 4 hours in room temperature

Boxed Warning Management of CRS and ICANS

- Consider management per current practice guidelines, for a full list visit elrexfiorems.com/#Main under "Adverse Reaction Management Guide"
    - Patients should be hospitalized for 48 hours after the first step-up dose and for 24 hours after the second, due to CRS risk
    - CRS symptoms can range from fever, hypoxia, and chills to hypotension, tachycardia, headaches, and hepatotoxicity
    - Neurologic Toxicity Including ICANS common symptoms: headaches, encephalopathy, motor dysfunction, and sensory neuropathy
    - At the first sign of CRS or neurologic toxicity withhold elranatamab until symptoms resolve, or permanently discontinue it depending on the severity
        - Tocilizumab should be considered for a temperature of ≥100.4 °F/38°C alone if not related to any other cause (grade 1) and is recommended for grade ≥2 CRS
        - Dexamethasone administration is recommended for grade ≥2 ICANS
        - Monitor vital signs every 4 hours, daily organ review, physical exam, blood counts, metabolic and coagulation profiles, and measure CRP and ferritin levels
- Other common adverse events: fatigue, injection-site reaction, pyrexia, GI disorders, skin and respiratory issues

Patient Centered Activities:

- Material may be provided to the patients to help identify serious and non-serious AEs
    - Patient booklet for education and assessment monitoring of CRS/ICANS
    - Pulse oximeter, thermometer, and automatic blood pressure monitor
    - Teach patients/caregivers to identify and manage CRS and ICANS symptoms
        - Caregivers are expected to inform provider team if the patient experiences any concerning

symptoms and to bring their treatment card/booklet to all clinic visits, as required by REMS
        - Look for common CRS/ICANS symptoms ranging from fever, hypoxia, and chills to hypotension, tachycardia, headaches, hepatotoxicity, encephalopathy, motor dysfunction, and sensory neuropathy
    - Seek medical help if you experience any unusual symptoms for a full list of symptoms
    - Advise against driving or operating machinery for 48 hours post each step-up dose and if neurological symptoms arise
- Post-ramp up administration guidelines
    - Outpatient treatment should be within 60 minutes of a hospital
    - Utilize triage which involves using a standard assessment in the electronic health record (EHR) to evaluate and record signs of CRS and ICANS
    - Comprehensive patient hand-off should take place for patients returning back to referral sites
- Patient financial assistance: NCODA Financial Assistance Tool, Support & financial resources, Co-pay assistance

References:

1. Elrexfio (elranatamab-bcmm) Prescribing Information.
2. Lesokhin AM, Tomasson MH, Bertrand Arnulf, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nature Medicine. Published online August 15, 2023. doi:https://doi.org/10.1038/s41591-023-02528-9.
3. Prince HM, Bahlis NJ, Rodriguez-Otero P, et al. MagnetisMM-3: Long-term update and efficacy and safety of less frequent dosing of elranatamab in patients with relapsed or refractory multiple myeloma. Poster presented at ASH; December 2024; San Diego, CA.
4. Martin TG, Mateos MV, Nooka A, et al. Detailed overview of incidence and management of cytokine release syndrome observed with teclistamab in the MajesTEC-1 study of patients with relapsed/refractory multiple myeloma. Cancer. 2023;129(13):2035-2046. doi:10.1002/cncr.34756.
5. U.S. Food and Drug Administration. What's REMS. Accessed February 5, 2024. Available from: https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/whats-remsTH.