



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

Description:

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

Background: Elranatamab-bcmm (Elrexfio™) is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.¹ The phase 2 MagnetisMM-3 trial, confirmed objective response rate (ORR) of 61% and complete response (CR) or better of 35%. Fifty responders switched to biweekly dosing and forty improved or maintained their response for ≥ 6 months. A median follow-up of 14.7 months, median duration of response (mDOR), progression-free survival (PFS), and overall survival (OS) had not been reached at the time of primary publication.² After a median long-term follow-up of 17.6 months, 26.8% of patients remained on treatment. The confirmed ORR was 61% (95% CI, 51.8-69.6), with 37.4% of patients achieving CR or better. Among evaluable patients (those with ≥CR and evaluable for minimal residual disease (MRD)), 90% achieved MRD negativity. mDOR has not been reached. The probability of maintaining a response at 18 months was 68.8% (95% CI, 56.5-78.2), the median PFS was 17.2 months (95% CI, 9.8-NE), and median OS at 21.9 months (not yet matured).^{3,4} Pooled analysis of patients with prior BCMA treatment showed elranatamab monotherapy was efficacious in patients with RRMM and prior exposure to BCMA-directed therapy (ADC and/or CAR-T) with ORR 46%, with early, deep, and durable responses with a mDOR, 17.1 months (prior CAR-T treatment, ORR 52.8% and mDOR not reached; prior ADC treatment ORR was 42.4% and mDOR 13.6 months). With a median follow-up of 11.3 months, median PFS was 5.5 months and median OS was 12.1 months (prior CAR-T treatment, median PFS was 10.0 months and median OS was 12.1 months; prior ADC treatment, median PFS was 3.9 months; median OS was 12.1 months).⁵ Treatment-emergent adverse events (TEAEs) seen were cytokine release syndrome, neutropenia, anemia, diarrhea, fatigue, decreased appetite, pyrexia, cough, nausea, thrombocytopenia, lymphopenia, injection site reaction, hypokalemia, and leukopenia. TEAEs of special interest included immune effector cell-associated neurotoxicity syndrome (ICANS) and infection.⁴ Lastly, there continue to be therapy sequencing debates with T-cell engaging therapies. T-cell exhaustion following CAR-T and bispecific antibody treatment is a concern for subsequent T-cell engaging treatment. An account of previous therapies should be considered when selecting patients for bispecific antibody treatment.

PQI Process:^{1, 2, 7}

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 ICANS⁶
- 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.

- Prepare for REMS audit by maintaining electronic records of all staff REMS training and product dispensation

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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 (48 hours after step-up dose 1, and for 24 hours after step-up dose 2) 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** (see Supplemental Information for dosing)⁵
 - **Bacterial:** Prophylaxis includes levofloxacin/ciprofloxacin: Start when ANC ≤ 0.5 K/mcL or ANC < 1.0 K/mcL is expected to last ≥ 7 days and 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 and 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 Effects⁴

Dosing Calendar Elranatamab (Elrexfio®)	Week 1: Step Up doses		Week 2: Treatment	Week 3 onwards: Treatments	Biweekly (Every 2 Weeks)
	Day 1	Day 4	Day 8	Once weekly from day 8* <small>*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</small>	Week 25 and every 2 weeks
	12 mg	32 mg	76 mg	76 mg weekly	76 mg biweekly
	0.3 mL SQ	0.8 mL SQ	1.9 mL SQ	1.9 mL SQ weekly	1.9 mL SQ biweekly <small>*Patients may transition to every 4 week dosing after ≥ 6 biweekly cycles</small>

- 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 elrexfioems.com 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. Tomasson M, Iida S, Niesvizky R, et al. Long-Term Efficacy and Safety of Elranatamab Monotherapy in the Phase 2 MagnetisMM-3 Trial in Relapsed or Refractory Multiple Myeloma (RRMM). *Blood*. 2023;142(Supplement 1):3385-3385. doi:<https://doi.org/10.1182/blood-2023-182130>.
4. Tomasson M, Iida S, Niesvizky R, et al. Long-Term Efficacy and Safety of Elranatamab Monotherapy in the Phase 2 MagnetisMM-3 Trial in Relapsed or Refractory Multiple Myeloma; Poster presented at ASH 2023.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections V.2.2023.
6. 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-rems>.
7. 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.

Supplemental Information

Antimicrobial prophylaxis and infection prevention Dosing⁵

- Bacterial
 - Ciprofloxacin 500–750 mg PO every 12 hours or 400 mg IV every 8–12 hours
 - Levofloxacin 500–750 mg PO or IV daily
- Fungal
 - Fluconazole In adults with normal renal function: typical dosing is 400 mg IV/PO daily (may vary)
 - Posaconazole Loading dose 300 mg DR tablet PO BID or 300 mg IV BID on Day 1 and then 300 mg PO daily
 - Voriconazole 200 mg PO BID or 4 mg/kg IV BID
 - Isavuconazole Loading dose 372 mg IV/ PO every 8 hours x 6 doses then 372 mg IV/PO daily
- HSV/VZV
 - Valacyclovir 500 mg PO BID
 - Acyclovir HSV 400–800 mg PO BID; VZV in allogeneic HCT recipients 400– 800 mg PO BID
- PJP
 - TMP-SMZ Single strength daily or double strength 3 times per week
 - Dapsone 100mg PO daily or 50 mg BID
 - Atovaquone 1.5 g PO daily