# Elranatamab (Multiple Myeloma)

**Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk**

## Index



## Indication

Treatment of relapsed and refractory multiple myeloma after 3 or more lines of treatment (including an immunomodulatory agent (IMID), proteasome inhibitor (PI) and anti-CD38 antibody) when the myeloma has progressed on the last treatment when pomalidomide plus dexamethasone would otherwise be offered.

(CDF)

**Response Rates**

Phase II MagnetisMM 3 study

- Single agent Elranatamab in patients refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 antibody with relapsed or refractory disease to last line of treatment
- ORR: 61% (35% CR or greater, 56.1% VGPR or greater)
- PFS & OS not reached at 14.7 months.
- At 15 months median DOR, PFS and OS were 71.5%, 50.9% and 56.7% respectively

## Regimen details

**Cycle 1**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1* | Elranatamab | 12mg | SC |
| 4* | Elranatamab | 32mg | SC |
| 8, 15 & 22 | Elranatamab | 76mg | SC |

*Patients should be monitored for cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) for 48hours after step-up doses on day 1 and day 4. Patients should remain within the proximity of a healthcare facility or be treated as an inpatient during this period. The minimum dose interval between two doses is 48 hours.

**Cycles 2-6**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1, 8, 15 & 22 | Elranatamab | 76mg | SC |

**Cycle 7 onwards**

| Day | Drug | Dose | Route |
|---|---|---|---|
| D1 &15 | Elranatamab | 76mg | SC |

### Cycle frequency
28 days

### Number of cycles
Until disease progression or unacceptable toxicity

### Pre-medication
Required for cycle 1 days 1, 4 and 8. 1 hour prior to Elranatamab subcutaneous injection:

- Paracetamol 1g PO
- Chlorphenamine 10mg IV/ 4mg PO
- Dexamethasone 20mg IV/PO

If any grade 2 or 3 CRS consider continuing premedication for future doses.

### Supportive medication
Cycle 1 days 1-8: Omeprazole 20mg od, consider ongoing treatment as indicated.
Cycle 1 only days 1-7: Allopurinol 300 mg OD (100mg OD if CrCl < 20mL/min)
Cycle 1 only days 1-14: Paracetamol 1g qds/prn
Cycles 1-3: Levofloxacin 500mg OD (reduced dose if CrCl <50ml/min)
All cycles: Antiviral prophylaxis as per local policy and continue until off treatment for > 3 months
All cycles: Prophylactic co-trimoxazole 480mg bd on Mon, Weds, Fri until CD4 count >200/microL
All cycles: metoclopramide 10mg TDS prn
Hep B virus treatment entecavir: screen for virus prior to treatment and start if positive hep B PCR.
Ganciclovir/valganciclovir: if positive CMV PCR with CMV related organ disease. Monitor the viral load.
Bisphosphonates as per local policy
IVIg monthly when total IgG <4g/L. Recommended dose of IVIg: 0.4-0.6g/kg/month to achieve a trough level of at least the lower limit of the age-specific reference range. Continue when off treatment until IgG >4g/L as per NHSE policy

## Emetogenicity
Low risk

## Administration
Inject into the subcutaneous tissue of the abdomen (preferred) or, alternatively, it may be injected into the subcutaneous tissue of the thigh. Do not press or rub the site of injection. Do not inject into areas where the skin is red, bruised, tender, hard or areas where there are scars.

A minimum of 2 days should be maintained between step up dose 1 (12mg) and 2 (32mg) and a minimum of 3 days should be maintained between step up dose 2 (32mg) and the first full treatment dose (76mg). A minimum of 6 days should be maintained between weekly doses.

If a dose is delayed, treatment should be restarted according to the table below, based on last dose administered and length of delay:

| **Last dose administered** | **Duration of delay from last dose administered** | **Action** |
|---|---|---|
| Step-up dose 1 (12mg) | ≤ 14 days | Continue usual schedule with step-up dose 2 (32 mg)*. If tolerated, increase to 76 mg 4 days later. |
| | > 14 days | Restart step-up dosing schedule at step up dose 1 (12mg)*. |
| Step-up dose 2 (32mg) | ≤ 14 days | Continue usual schedule with 76mg dose |
| | 15 - ≤ 28 days | Restart at step-up dose 2 (32mg)*. If tolerated increase to 76mg 1 week later. |
| | > 28 days | Restart step-up dosing schedule at step up dose 1 (12mg)*. |
| Any full dose treatment (76mg) | ≤ 42 days | Continue usual schedule with 76mg dose |
| | 43 - ≤ 84 days | Restart at step-up dose 2 (32mg)*. If tolerated increase to 76mg 1 week later. |
| | > 84 days | Restart step-up dosing schedule at step up dose 1 (12mg)*. |

*Premedication required as described above.

## Extravasation
N/A

## Mandatory investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| Renal profile (U&Es including creatinine) | 14 days |
| Liver profile (ALT/AST, ALP, bilirubin, albumin) | 14 days |
| Clotting screen | 14 days |
| Virology (Hep B/C, HIV, CMV (incl. PCR), EBV (incl. PCR)) | 3 months |
| Immunoglobulins | 14 days |

## Additional investigations advised pre-first cycle

- HBA1C
- Serum protein electrophoresis
- β2 microglobulin
- Bone profile (Calcium, phosphate, magnesium)
- CRP
- LDH
- Serum free light chains (SFLC)/Paraprotein (PP)
- Urine protein/creatinine ratio
- Bone marrow examination for cytogenetic analysis FISH
- Imaging as per local guidelines
- Annual flu, Covid-19 and pneumococcal vaccination

## Investigations – pre subsequent cycles

| Investigation | Validity period |
|---|---|
| FBC | 7 days* |
| Renal profile (U&Es including creatinine) | 7 days |
| Liver profile (ALT/AST, ALP, bilirubin) | 7 days |
| Immunoglobulins | 7 days |

*Check FBC weekly during first cycle if Hb < 90g/L, platelets < 50 or neutrophils < 1 at baseline

## Additional investigations advised pre subsequent cycles

- SFLC, PP – results are not required prior to administration of cycle
- Bone profile (Calcium, phosphate, magnesium)
- Viral PCRs inc EBV, CMV< (every 3 months)

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

| Investigation | Limit |
|---|---|
| Neutrophils | ≥ 0.5 x $10^9$/L |
| Platelets | ≥ 25 x $10^9$/L with no evidence of bleeding |
| Haemoglobin (Hb) | ≥ 80g/L |
| Creatinine Clearance (CrCl) | > 30ml/min |
| Bilirubin | < 1.5 x ULN (see below) |
| ALT/AST | < ULN (see below) |

## Dose modifications

Dose modifications are not recommended. Dose delays may be required to manage toxicities.

### Haematological toxicity

| Toxicity | Action |
|---|---|
| Hb <80g/l | Withold dose until Hb>80g/l or consider transfusion if disease related |
| Neutrophils <0.5 x $10^9$/L or febrile neutropenia | Withold dose until count ≥ 0.5 x $10^9$/L (or > 1.0 x $10^9$/L and resolution of fever if febrile neutropenia). Consider GCSF if disease related. |
| Platelets <25 x $10^9$/L *or* Platelets 25 -50 x $10^9$/L with bleeding | Withold dose until count ≥ 25 x $10^9$/L and no evidence of bleeding |

### Renal impairment

No dose adjustments are needed with mild to moderate renal impairment (eGFR ≥ 30ml/min). There is insufficient data in patients with severe renal impairment.

### Hepatic impairment

No dose adjustments are needed with mild hepatic impairment, defined as:

- bilirubin ≤ 1.5 x ULN and any ALT/AST
- bilirubin ≤ ULN and ALT/AST > ULN

There is insufficient data in patients with moderate/severe hepatic impairment.

### Other toxicities

| Toxicity | Definition | Dose adjustment |
|---|---|---|
| Cytokine release syndrome (CRS) | Any grade | If CRS is suspected, treatment should be withheld until adverse reaction resolves.<br>For recurrent or persistent (>48 hrs) Grade 3 or any Grade 4 CRS permanently discontinue elranatamabFor management of CRS see below. |
| Immune effector cell-associated neurotoxicity syndrome (ICANS) | Any grade | If ICANS is suspected, treatment should be withheld until adverse reaction resolves.<br>For recurrent or persistent (>48 hrs) Grade 3 or any Grade 4 ICANS permanently discontinue elranatamabFor management of ICANS see below. |
| Infection | Any grade | Withold dose until infection resolved |
| Other non-haematological toxicity | Grade 3-4 | Pause treatment and provide relevant supportive care. Once resolved to grade 1 or baseline, resume treatment.<br>Permanently discontinue if recovery does not occur. |

## Side Effects

### MagnetisMM 3 study:

| Toxicity | | Any grade (%) | Grade 3 or 4 (%) |
|---|---|---|---|
| **Haematological** | Anaemia | 48.8 | 37.4 |
| | Neutropenia | 48.8 | 48.8 |
| | Thrombocytopenia | 30.9 | 23.6 |
| | Lymphopenia | 26.8 | 25.2 |
| **Non-haematological** | Infections | 69.9 | 39.8 (+ 6.5% grade 5) |
| | Cytokine release syndrome | 57.7 | 0 |
| | Diarrhoea | 42.3 | 1.6 |
| | Fatigue | 36.6 | 3.3 |
| | Decreased appetite | 33.3 | 0.8 |
| | Pyrexia | 30.1 | 4.1 |
| | Covid-19 related | 29.3 | 15.4 |
| | Injection site reaction | 26.8 | 0 |
| | Nausea | 26.8 | 0 |
| | Hypokalemia | 26 | 10.6 |
| | Cough | 25.2 | 0 |
| | Headache | 23.6 | 0 |

**Treatment related mortality:** 11.4% (6.5% due to infections)

### Specific drug related side effects:

**Cytokine Release Syndrome**

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, may occur in patients receiving Elranatamab. The median time to onset is 2 days (range 1-9 days) and the median time to resolution is 2 days (range 1-19 days). Clinical signs and symptoms may include fever, hypoxia, chills, hypotension, tachycardia, headache and elevated liver enzymes. If CRS is suspected treatment should be withheld and the following investigations should be performed:

- FBC, U&Es, LFTs, bone profile, CRP, ferritin and coagulation screen, CXR and ECG

Management of CRS should be as the table below:

| Grade | Symptoms | Management |
|---|---|---|
| 1 | Temp >38 °C<br>**AND**<br>no hypoxia or hypotension | • Monitor vital signs every 4 hours<br>• Treat as per neutropenic sepsis guidelines<br>• Consider early tocilizumab use<br>• If persistent fevers (>24-48 hrs), consider IV tocilizumab 8mg/kg (max 800mg) over 1 hr* |
| 2 | Temp >38 °C<br>**WITH**<br>hypotension responsive to fluids<br>**OR**<br>hypoxia requiring <6L/min O2 | • Monitor vital signs every 4 hours<br>• Treat as per neutropenic sepsis guidelines<br>• Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed*<br>• Consider IV methylprednisolone 1mg/kg bd<br>• Inform ICU/consider transfer<br>• Administer O2 and fluids |

| Grade | Symptoms | Management |
|---|---|---|
| 3 | Temp >38 °C<br>**WITH**<br>hypotension requiring vasopressors<br>**OR**<br>hypoxia requiring >6L/O2 | **TRANSFER TO ITU**<br>• Treat as per neutropenic sepsis guidelines<br>• Perform continuous cardiac monitoring and echo<br>• Administer vasopressors as required<br>• Administer O2 as required<br>• Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed*<br>• Administer IV methylprednisolone 1mg/kg bd<br>• If refractory, consider IV methylprednisolone 1g and/or alternative immunosuppressive agents (e.g. anakinra)<br>• For recurrent grade 3 CRS, permanently discontinue elranatamab. |
| 4 | Temp >38 °C<br>**WITH**<br>hypotension requiring multiple vasopressors<br>**OR**<br>hypoxia requiring CPAP/BiPAP/ventilation | **TRANSFER TO ITU**<br>• Treat as per neutropenic sepsis guidelines<br>• Perform continuous cardiac monitoring and echo<br>• Administer vasopressors<br>• Administer O2<br>• Administer IV tocilizumab 8mg/kg (max 800mg) over 1 hr, repeat every 8 hours as needed*<br>• Administer IV methylprednisolone 1g OD and/or alternative immunosuppressive agents (e.g. anakinra)<br>• Permanently discontinue elranatamab |

* Max 3 doses in a 24 hours period, maximum total of 4 doses.

**Immune Effector Cell Neurotoxicity Syndrome (ICANS)**

Immune effector cell neurotoxicity syndrome (ICANS) is a potential neurological complication seen in patients receiving Elranatamab. The incidence of ICANS with Elranatamab is reported to be 3.4%, with all events being grade 1 or 2. Clinical signs of ICANS can include a change in cognitive state, fall in GCS and seizures.

**ICANS monitoring**

- Check ICE score using ICE assessment tool, prior to receiving Elranatamab
- Check ICE score twice a day whilst an inpatient and twice a day for 48 hours as an outpatient for the first cycle
- If grade 2 or higher ICANS experienced, patients should be monitored as an inpatient for 48 hours following the next dose.
- If ICANS is suspected a neurological examination should be performed, in addition to the following investigations:
  - ECG
  - Three times a day ICE assessment
  - MRI brain/CT brain
  - Consider diagnostic lumbar puncture

**ICE assessment tool**

| | Question | Points |
|---|---|---|
| 1 | Which year is it? | 1 |
| 2 | Which month is it? | 1 |
| 3 | Which city/town are we in? | 1 |
| 4 | Which hospital are we in? | 1 |
| 5 | Follow an instruction<br>e.g. touch your nose, lift your right arm, shrug your shoulders | 1 |
| 6 | Name 3 objects<br>Point to three different objects | 3 |
| 7 | Write a sentence | 1 |
| 8 | Count backwards from 100 in 10's | 1 |

Management of ICANS should be as the table below, with grading based on score from the ICE assessment:

<table>
<tr><th rowspan="2">ICE score and symptoms</th><th colspan="2">Management</th></tr>
<tr><th>Monitoring/Investigations</th><th>Treatment</th></tr>
<tr><td>Score 10</td><td colspan="2">No ICANS present</td></tr>
<tr><td>Grade 1 - Score 7-9<br>Awakes spontaneously</td><td rowspan="2">Score 3-9<ul><li>Three times a day ICE score</li><li>Regular neurological observations</li><li>Consider tocilizumab if concurrent CRS</li></ul></td><td>Score 7-9<ul><li>If persistent symptoms (>48 hrs), consider IV dexamethasone (10mg qds) until resolution, then taper</li><li>Consider seizure prophylaxis*</li></ul></td></tr>
<tr><td>Grade 2 - Score 3-6<br>Awakes to voice</td><td>Score 3-6<ul><li>Administer IV dexamethasone (10mg qds) until resolution to grade 1 or less, then taper</li><li>Administer antiepileptics</li><li>Consider EEG and imaging</li></ul></td></tr>
<tr><td>Grade 3 - Score 0-2 AND<br>Awakes to tactile stimuli<br>Seizures resolve rapidly<br>Focal cerebral oedema on imaging</td><td rowspan="2">Score 0-2<br>TRANSFER TO ICU<ul><li>Regular neurological observations</li><li>Three times a day ICE score</li><li>Perform neuroimaging and EEG</li><li>Administer antiepileptics</li><li>Consider CSF evaluation for other causes/pressure measurement</li><li>Consider tocilizumab if concurrent CRS</li></ul></td><td>Score 0-2 and rousable<ul><li>Administer IV dexamethasone (10mg qds) until resolution to grade 1 or less, then taper</li><li>If refractory consider IV methyl prednisolone 1g daily for 3 days. Taper when symptoms improve</li></ul></td></tr>
<tr><td>Grade 4 - Score 0 AND<br>Unrousable<br>Prolonged (>5 min) or frequent seizures<br>Motor weakness<br>Diffuse cerebral oedema on imaging</td><td>Score 0 and unrousable<ul><li>Administer IV methylprednisolone 1g daily for 3 days. Taper when symptoms improve</li><li>For refractory patients consider alternative therapies (e.g. anakinra)</li></ul></td></tr>
</table>

*Seizure prophylaxis includes levetiracetam 500mg po/IV bd, up to 2000mg bd

**Infections**

Infections occurred in approximately 70% of trial patients with approx. 40% being grade 3 and above. 6.5% experienced fatal infections. 98.6% of patients experienced immunoparesis at baseline and 75.5% had an IgG <400mg/dl at least once during treatment. 43.1% of patients received immunoglobulin replacement whilst on trial. Of note, the incidence of severe infections decreases when switching to fortnightly doses (from cycle 7)

The infections reported in >5% of patients were as follows:

| No of pts (%) | Any grade (%) | Maximum grade 3 or 4 (%) | Grade 5 (%) |
|---|---|---|---|
| **Covid 19 related** | 29.3 | 15.4 | 1.6 |
| **pneumonia** | 16.3 | 8.1 | 0 |
| **URTI** | 16.3 | 0 | 0 |
| **Sinusitis** | 10.6 | 1.6 | 0 |
| **UTI** | 9.8 | 3.3 | 0 |
| **Sepsis** | 6.5 | 6.5 | 0 |
| **Bacteraemia** | 5.7 | 1.6 | 0 |
| **CMV reactivation** | 5.7 | 1.6 | 0 |

## Additional information

Not applicable

## Significant drug interactions – for full details consult product literature/ reference texts

No formal drug interactions have been identified. Based on in vitro and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions.

**CYP450 substrates with narrow therapeutic index:** transient elevation of proinflammatory cytokines when starting treatment with elranatamab may suppress CYP450 activities, consider therapeutic monitoring of substrate.

## References


- Rodriguez-Otero et al. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. Lancet. 2024;25:e205-16
- Lesokhin et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 magnetisMM-3 trail results. Nature Medicine 2023;29:2259-2267
- Summary of Product Characteristics Elranatamab (Pfizer) accessed 1 August 2024 via www.medicines.org.uk
- National Institute for Health and Care Excellence – Draft guidance – ID4026. Accessed 1 August 2024 via www.nice.org.uk

| Version | Issue date | Review date | Revision | Written/Checked/Authorised |
|---|---|---|---|---|
| 1 | Aug 2024 | Aug 2027 | New protocol | Written: Dr S Moore (Consultant Haematologist, UHBW NHS Trust)<br>Checked: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)<br>Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance) |
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