Indication	For induction and consolidation therapy of transplant-eligible multiple myeloma not previously treated with any systemic anti-cancer therapy, except emergency corticosteroids prior to this treatment. NB NHS England does not fund daratumumab for patients with primary amyloidosis.
Treatment Intent	Disease modification
Frequency and number of cycles	**INDUCTION cycle 1-4** Cycle 1 and 2 every 28 days: weekly daratumumab (total 8 doses) Cycle 3 and 4 every 28 days: 2 weekly daratumumab (total 4 doses) Followed by a pause for high-dose chemotherapy and stem cell transplantation **CONSOLIDATION cycle 5-6** Cycle 5 and 6 every 28 days: 2 weekly daratumumab (total 4 doses) NB the first administration of daratumumab can be given in split doses on different days if IV infusion is used instead of subcutaneous daratumumab. A formal medical review **MUST** occur by the end of the second 4-weekly cycle of treatment to establish whether treatment should continue.

Monitoring Parameters pre-treatment	• **Thalidomide Prescription Authorisation Form must be completed at the time of prescribing**
	• Check virology status prior to cycle 1.
	• Consider flu and pneumococcal vaccination pre-therapy.
	• Monitor FBC before each cycle, on Day 8, Day 15 and day 22 cycles 1 and 2 and on Day 1 and Day 8 of cycles 3-6. Proceed when neutrophils > 0.5 x 10^9/L and platelets > 25 x 10^9/L.
	• U&Es & LFTs at each cycle.
	• BP baseline and if clinically indicated thereafter.
	• Lung function assessment required in patients with pre-existing respiratory disease (COPD, asthma) and heavy smokers. Clinician to decide if further imaging required in patients with additional co-morbidities.
	• Blood glucose every cycle.
	• ECG baseline and if clinically indicated thereafter.
	• Ensure patient is well hydrated (drinking ~3L/day) prior to treatment.
	• Limited data of daratumumab SC in patients >120kg, give at clinicians' discretion.
	• **Supportive medication:** Review TTOs and from cycle 2 prescribe allopurinol and/or loperamide as required.
	• **Hepatic impairment:**
	  ○ Daratumumab: No dose adjustments necessary.
	  ○ Bortezomib: Consider dose reduction in moderate/severe hepatic impairment (Bilirubin >1.5ULN), reduce Bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
	  ○ Thalidomide: No specific dose recommendations.
	• **Renal impairment:**
	  ○ Daratumumab: No dose adjustments necessary.
	  ○ Bortezomib: CrCl < 20ml/min discuss with consultant.

- Thalidomide: No specific dose recommendations.

- **Daratumumab injection related reactions (IRRs**):
- Daratumumab can cause severe injection reactions which may result in admission to hospital. Pre-meds must be given 1-3 hours before the injection.
- Patients should be pre-medicated with chlorphenamine, dexamethasone and paracetamol as well as monitored (vital signs before and after the injection) and counselled regarding IRRs, especially during and following the first and second injections.
  If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. Daratumumab therapy should be discontinued immediately and permanently.
  Patients should be observed for 6 hours post the 1st injection, 2 hours after 2nd dose and then 15 minutes observation after subsequent doses.
- The use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur.
- **Administration of sub cut daratumumab:**
- Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections.
- Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, and hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.
- **Drug specific cautions and dose adjustments:**
- **Thalidomide:**
  - Thromboembolism: patients have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism. Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors.
  - If renal impairment restricts use of thromboprophylaxis in at risk patients consider withholding thalidomide.
  - Peripheral neuropathy: Patients should be advised to report prickling, numbness and paraesthesia. It is recommended that clinical and neurological examinations are performed in patients prior to starting thalidomide therapy, and that routine monitoring is carried out regularly during treatment.
  - Skin toxicity: Interruption or discontinuation of thalidomide should be considered for any Grade 2-3 skin rash. Thalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) is suspected and should not be resumed following discontinuation for these reactions.
  - Tumour lysis syndrome (TLS): Patients with a high tumour burden are at greater risk of TLS, these patients should be monitored closely.
  - Non-haematological - Grade 3-4 Thalidomide toxicity (constipation, neuropathy, fatigue, sedation, rash, tremor and oedema). Stop Thalidomide for the remainder of the cycle and then reintroduce at 50mg daily with the subsequent cycle.
  - **Dose modification** for thalidomide induced peripheral neuropathy.

Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function, continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen.
Grade 2 (interfering with function but not with activities of daily living), Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living) or **Grade 4** (neuropathy which is disabling), discontinue treatment.

- **Bortezomib:**
  - Use with caution in patients with pre-existing heart disease or with high risk factors.
  - Patients should be advised to report any new or worsening respiratory symptoms.
  - Bortezomib can affect the ability to drive and use machines. If patients experience fatigue/dizziness or blurred vision they should not drive.
  - At least 72 hours must elapse between consecutive Bortezomib doses.
  - **Dose modification bortezomib:** If Hb < 65g/l transfuse patient and restart treatment when Hb >65g/l.
  - Bortezomib should be withheld for any grade 3 non-haematological (see below for guidance on managing neuropathic toxicities) or Grade 4 haematological toxicities (neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L); once toxicity has settled reinitiate at 75%, (ie 1.3mg/m^2 → 1.0mg/m^2 → 0.7mg/m^2).
  - For Neuropathic Pain and or Peripheral Sensory or Motor Neuropathy dose reductions see table 1.
- **Dexamethasone:**
  - Dose reduction may be considered in patients who are >75 years, patients who have a BMI <18.5, patients with poorly controlled diabetes mellitus or who have had prior intolerance/adverse event (AE) to steroid therapy.
- **Interference with tests (refer to company risk materials):** Daratumumab binds to CD38 on red blood cells and results in a positive Indirect Antiglobulin Test (Coombs test) which may persist for up to 6 months after the last infusion. Send a blood sample for group/ direct antiglobulin/phenotype testing prior to treatment. Daratumumab may be detected on SPE and IFE assays resulting in false positive results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses.
- **Common drug interactions: (for comprehensive list refer to BNF/SPC)**
  The concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced. CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) should be used with caution and patients monitored for toxicity.
- **Contraception:**
  Follow thalidomide pregnancy prevention programme. Ensure patient is informed of requirement for strict contraception precautions during treatment with thalidomide.
  To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 8 months after cessation of daratumumab and bortezomib treatment.
  Male patients should use effective contraceptive measures during treatment and be advised not to father a child while receiving bortezomib and for 5 months following completion of treatment.
- **Missed dose:**

	○ Daratumumab: If a planned dose is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval. ○ Thalidomide: If less than 12 hours since the missed dose patients should take the dose, if more than 12 hours the patient should be advised to omit the dose and continue with their normal schedule the following day. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	HAEM-MYEL-046 V1 SPC accessed online 23.10.2024

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Dose modification of bortezomib for neuropathic toxicities

Severity of Peripheral Neuropathy Signs and Symptoms*	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia) without pain or loss of function	No Action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**)	Reduce bortezomib to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ***)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib
*Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 **Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc; ***Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	

INDUCTION - Cycle 1 and 2 only: 28-day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	Montelukast **Cycle 1 day 1 only**	10mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
	BORTEZOMIB	**1.3mg/m^2**	SC	bolus	
4	**BORTEZOMIB**	**1.3mg/m^2**	SC	bolus	
8	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
	BORTEZOMIB	**1.3mg/m^2**	SC	bolus	
11	**BORTEZOMIB**	**1.3mg/m^2**	SC	bolus	
15 & 22	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections

TTOs cycle 1 and 2

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**40mg**	PO	OM on days 2, 9, 16 and 23 Take with or after food.
	THALIDOMIDE	**50mg–100mg**	PO	50mg ON **cycle 1**. Increase to 100mg from **cycle 2** if tolerated.
	Allopurinol	300mg	PO	OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	Omeprazole	20mg	PO	OD
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, and then prescribe as required.
	Consider prophylactic anticoagulation and antifungals			

INDUCTION - Cycle 3 and 4 only: 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
	BORTEZOMIB	**1.3mg/m^2**	SC	bolus	
4, 8 &11	**BORTEZOMIB**	**1.3mg/m^2**	SC	bolus	
15	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**40mg**	PO	OM day 2 Take with or after food.
	DEXAMETHASONE	**20mg**	PO	OM day 8, 9 and 16 Take with or after food.
	THALIDOMIDE	**50mg-100mg**	PO	ON
	Omeprazole	20mg	PO	OD
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, and then prescribe as required.
	Consider prophylactic anticoagulation and antifungals.			

CONSOLIDATION: Cycle 5 and 6: 28-day cycle

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections
	BORTEZOMIB	**1.3mg/m^2**	SC	bolus	
4, 8 &11	**BORTEZOMIB**	**1.3mg/m^2**	SC	bolus	
15	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Chlorphenamine	4mg	PO	stat	
	Paracetamol	1gm	PO	stat	
	DARATUMUMAB	**1800mg**	SC	3-5mins	Inject 15 mL into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject at other sites of the body as no data are available. Injection sites should be rotated for successive injections

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**20mg**	PO	OM day 2, 8, 9 and 16 Take with or after food.
	THALIDOMIDE	**50mg-100mg**	PO	ON
	Omeprazole	20mg	PO	OD
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Metoclopramide	10mg	PO	TDS for 3 days, then TDS PRN. Do not take for more than 5 days consecutively.
	Loperamide	2mg	PO	Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day). Dispense on Cycle 1 only, and then prescribe as required.
	Consider prophylactic anticoagulation and antifungals			