Indication	The treatment of relapsed or refractory multiple myeloma following 3 prior lines of systemic treatment to include a proteosome inhibitor and an immunomodulatory agent. The patient must not have been previously treated with daratumumab or an anti-CD38 antibody, unless they have been previously treated with daratumumab as part of induction therapy pre-transplant and must have responded to that daratumumab-containing combination. NB: Induction chemotherapy and stem cell transplant is considered to be 1 line of therapy. NB NHS England does not fund daratumumab for patients with amyloidosis unless they have a proven diagnosis of progressive myeloma and also an associated diagnosis of amyloidosis.
Treatment Intent	Disease Modification
Frequency and number of cycles	Every 28 days. Continue until progressive disease or unacceptable toxicity or patient choice, whichever occurs first.
Monitoring parameters pre-treatment	• Check virology status prior to cycle 1 • Consider flu and pneumococcal vaccination pre-therapy • Monitor FBC, U&Es, & LFTs at each cycle • No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. • **Renal or hepatic impairment:** No dose adjustments necessary • **Interference with tests:** 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. • **Contraception:** To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment • If a planned dose of daratumumab is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval. Daratumumab infusion rate and infusion related reactions (IRRs): • Daratumumab can cause severe infusion reactions which may result in admission to hospital. Pre-meds must be given 1-3 hours before the infusion and patients must be monitored during the entire infusion. For patients that experience any Grade IRRs, continue monitoring post-infusion until symptoms resolve. • For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. • 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. • Grade 1-2 IRR (mild to moderate): Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at

	increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour. • Grade 3 IRR (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate. The procedure should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction. • Grade 4 IRR (life-threatening): Permanently discontinue daratumumab treatment • Infusion rate of first infusion (diluted in 1000ml): Administer at 50 ml/hr for the first hour. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 ml/hr every hour to a maximum rate of 200ml/hr. • Infusion rate of week 2 infusion (diluted in 500ml*) ***NB: This rate should also be used for split dose administration***. Administer at 50 ml/hr for the first hour. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 ml/hr every hour to a maximum rate of 200ml/hr. • Infusion rate of subsequent (week 3 onwards) infusions** (diluted in 500ml*): Administer at 100 ml/hr for the first hour. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 ml/hr every hour to a maximum rate of 200ml/hr. • *NB: With the exception of split dose, a dilution volume of 500 mL should be used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous week. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion. • NB**A modified initial rate for subsequent infusions (week three onwards) should only be used if there were no >/= Grade 1 IRRs during the previous infusions. Otherwise, use instructions for the week 2 infusion rate. • **Daratumumab rapid rate infusion** The rapid rate of infusion is unlicensed. Patient consent must be obtained. Inclusion criteria: o Patients on CYCLE 2 onwards and have received and tolerated 500ml daratumumab infusion at the licensed rate (see above) without ≥Grade 1 IRR's. o Daratumumab when used as monotherapy only. Exclusion criteria: o Previous >/=grade 3 infusion related toxicity with daratumumab. o IRR >/=Grade 1 with the most recent daratumumab infusion given at the standard manufacturer licensed rate. o Patients whose most recent dose was prepared in 1000ml dilution due to moderate or severe IRR. Patients must demonstrate tolerability of 500ml infusion rate at the standard rate. o Cardiac amyloid patients. Monitoring Parameters for rapid rate infusion: o Check vital signs before the start of infusion, then every 15min for the first hour and at the end of the infusion. o Monitor patients closely for adverse effects. Following the first rapid rate infusion patients should be monitored in the treatment unit for 30 min after the infusion has finished.

	○ **CAUTION:** Pre-existing COPD increases the risk of developing bronchospasm with daratumumab rapid infusion. Patients with COPD, asthma, other respiratory comorbidities and uncontrolled hypertension should be discussed with the clinician. For patients with a history of COPD or asthma administer post infusion short and long acting bronchodilators, and inhaled corticosteroids. During administration of rapid rate infusion these patients must be closely monitored throughout. • Sodium content: Each 20ml daratumumab (400mg) contains 1.6mmol sodium. • **Split dose administration** The first prescribed 16 mg/kg dose at week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively (see below)
Reference(s)	KMCC protocol HAEM-MYEL-036 V3 SmPC accessed online 14.01.2022 Lokhorst et al (2015) NEJM Lonial et al (2016) The Lancet Usmani (2016) The Blood Journal Thames Valley Rapid rate infusion protocol MM.48v1.0 St Lukes Cancer alliance Daratumumab Protocol v1.0

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

Dosing schedule for daratumumab (28-day cycle)

Cycle	Daratumumab due on day:
1	1, 8, 15 &22 NB day 1 of cycle 1 may be given as split dose
2	1, 8, 15 &22
3	1 & 15
4	1 & 15
5	1 & 15
6	1 & 15
7 onwards	1

A formal medical review as to whether treatment with daratumumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment

Standard administration of daratumumab - see below for alternative administration schedules.

Day	Drug	Dose	Route	Infusion Duration	Administration Details
Initial Daratumumab Infusion	Dexamethasone	20mg	IV		To be administered 1-3 hours prior to daratumumab.
	Paracetamol	1g	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Montelukast **Cycle 1 only**	10mg	PO	stat	
	DARATUMUMAB	**16mg/kg**	IV inf	See notes	Give via in-line 0.22 micrometre filter. In 1000ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
Second daratumumab infusion	Dexamethasone	20mg	IV / PO		To be administered 1-3 hours prior to daratumumab.
	Paracetamol	1g	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	DARATUMUMAB	**16mg/kg**	IV inf	See notes	Give via in-line 0.22 micrometre filter. May be given in 500 mL sodium chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous week. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion. Flush line pre and post infusion with Sodium Chloride 0.9%
Subsequent daratumumab infusions	Dexamethasone	12mg	IV / PO		To be administered 1-3 hours prior to daratumumab.
	Paracetamol	1g	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	DARATUMUMAB	**16mg/kg**	IV inf	See notes	Give via in-line 0.22 micrometre filter. May be given in 500 mL sodium chloride 0.9% only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous week. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion. Flush line pre and post infusion with Sodium Chloride 0.9%

Split dose daratumumab – Day 1 and 2, Cycle 1 ONLY as an alternative to standard administration

Day	Drug	Dose	Route	Infusion duration	Administration details
Cycle 1 Day 1	Dexamethasone	20mg	IV		To be administered 1-3 hours prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Montelukast **Cycle 1 only**	10mg	PO	stat	
	DARATUMUMAB	**8mg/kg**	IV	See notes	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
Cycle 1 Day 2	Dexamethasone	20mg	IV/PO		To be administered 1-3 hours prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	DARATUMUMAB	**8mg/kg**	IV	See notes	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%

Rapid infusion daratumumab – only from cycle 2 in patients meeting inclusion criteria (see above)

Day	Drug	Dose	Route	Infusion duration	Administration details
Daratumumab rapid rate infusion	Dexamethasone*	20mg	IV		To be administered 1 hour prior to daratumumab infusion.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Montelukast	10mg	PO	**First rapid infusion only**	
	DARATUMUMAB	**16mg/kg**	IV	**100ml** over **30min** then infuse the remaining **400ml** over **60min** (ie 90 minutes in total)	Give via in-line 0.22 micrometre filter in 500ml sodium chloride 0.9% Flush line pre and post infusion with Sodium Chloride 0.9%
	***from 3rd infusion dexamethasone may be reduced to 12mg IV/PO**				
	NB: For patients with a history of COPD or asthma administer post infusion short and long acting bronchodilators, and inhaled corticosteroids.				

TTOs

TTOs	Drug	Dose	Route	Directions
Following each infusion of daratumumab	Dexamethasone	4mg	po	To be taken in the morning for 2 days starting the day after daratumumab treatment (for split dose start on day 3)
	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)
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last treatment dose)
	Allopurinol	300mg	PO	OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	Omeprazole	20mg	PO	OD
	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously. On Cycle 1 only, then prescribe as required
	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, then prescribe as required.