Indication	Relapsed multiple myeloma in patients who have received one prior line of treatment. The patient must either have not received bortezomib previously, or shown no disease progression whilst receiving bortezomib.
Treatment Intent	Disease modification
Frequency and number of cycles	Every 21 days cycle 1 to 8, then every 28 days from cycle 9. Bortezomib and dexamethasone should be stopped after 8 cycles. Continue daratumumab until progressive disease or unacceptable toxicity or patient choice, whichever occurs first. Bortezomib and dexamethasone treatment can be continued in the event daratumumab is permanently discontinued. A formal medical review **MUST** occur by the end of the first 6 weeks of treatment to establish whether treatment should continue.
Monitoring Parameters pre-treatment	• Check virology status prior to cycle 1 • Consider flu and pneumococcal vaccination pre-therapy. • Monitor FBC before each cycle and on Day 8. 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. • **<u>Dose reduction</u>** o Dose reductions of daratumumab are not recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. o 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. o Bortezomib: If Hb < 65g/l transfuse patient and restart treatment when Hb >65g/l. Bortezomib should be withheld for any grade 3 non-haematological (excluding neuropathy) or Grade 4 hematological 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/m2 → 1.0mg/m2 → 0.7mg/m2). For Neuropathic Pain and or Peripheral Sensory or Motor Neuropathy dose reductions see table 1. • **<u>Hepatic impairment</u>:** o Daratumumab: No dose adjustments necessary. o Bortezomib: Consider dose reduction in moderate/severe hepatic impairment (Bilirubin >1.5ULN), reduce Bortezomib to 0.7 mg/m2 in the first treatment

cycle. Consider dose escalation to 1.0 mg/m2 or further dose reduction to 0.5 mg/m2 in subsequent cycles based on patient tolerability.

- **Renal impairment:**
  - Daratumumab: No dose adjustments necessary.
  - Bortezomib: CrCl < 20ml/min discuss with consultant.

- **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.
- At least 72 hours must elapse between consecutive Bortezomib doses.
- 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.

- **Caution with 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.

- **Drug Interactions:** 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.

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 200mL/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 second infusion (diluted in 500ml*)**: 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 (3rd dose 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: A dilution volume of 500 mL should be used only if there were no ≥ Grade 1 infusion related reactions (IRR) with the previous dose. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion. • NB**A modified initial rate for subsequent infusions (3rd dose onwards) should only be used if there were no ≥ Grade 1 IRRs during the previous infusions. Otherwise, use instructions for the second dose infusion rate. • Sodium content: Each 20ml daratumumab (400mg) contains 1.6mmol sodium. • A formal medical review as to whether treatment with daratumumab/bortezomib/dex should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
References	KMCC protocol HAEM-MYEL-037v1, CDF list v1.137, SPC accessed online 20/06/19 Changes made in line with 'SOP for removal of ranitidine on KMCC protocols and on aria regimens'

NB For funding information, refer to the SACT funding spread sheet

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/m2
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/m2 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.	

Cycle 1 only 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	20mg	IV	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Montelukast	10mg	PO	stat	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	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%
	Bortezomib	**1.3mg/m2**	SC	bolus	
4	**Bortezomib**	**1.3mg/m2**	SC	bolus	
8	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	

Day 8 cont.	**Daratumumab**	**16mg/kg**	IV infusion	See notes above	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 dose. 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%
	Bortezomib	**1.3mg/m2**	SC	bolus	
11	**Bortezomib**	**1.3mg/m2**	SC	bolus	
15	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	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 dose. 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%

TTOs Cycle 1-3 only

TTO	Drug	Dose	Route	Directions
	Dexamethasone	20mg	PO	OM on days 2,4,5,9,11,12 and 16 (Where appropriate dose must be taken prior to bortezomib injection ie on days where bortezomib alone is administered)
	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)
	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 TDS for 3 days after bortezomib then 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.
	Consider the use of prophylactic anti-fungals			

Cycle 2 and 3: Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous dose. 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%
	Bortezomib	**1.3mg/m2**	SC	bolus	
4	**Bortezomib**	**1.3mg/m2**	SC	bolus	
8	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous dose. 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%
	Bortezomib	**1.3mg/m2**	SC	bolus	
11	**Bortezomib**	**1.3mg/m2**	SC	bolus	

15	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous dose. 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%

Cycle 4-8 repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	20mg	IV/PO	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion	See notes above	Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous dose. 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%
	Bortezomib	**1.3mg/m2**	SC	bolus	
4	**Bortezomib**	**1.3mg/m2**	SC	bolus	
8	**Bortezomib**	**1.3mg/m2**	SC	bolus	
11	**Bortezomib**	**1.3mg/m2**	SC	bolus	

TTOs cycle 4-8

TTO	Drug	Dose	Route	Directions
	Dexamethasone	20mg	PO	OM on days 2,4,5,8,9,11 and 12 (Where appropriate dose must be taken prior to bortezomib injection ie on days where bortezomib alone is administered)
	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)
	Omeprazole	20mg	PO	OD
	Metoclopramide	10mg	PO	Take 10mg TDS for 3 days after bortezomib then 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.
	Consider the use of prophylactic anti-fungals			

Cycle 9 onwards repeat every 28 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	12mg	PO/IV	stat	To be administered 1 hour prior to daratumumab.
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	10mg	IV	Slow bolus over 1 min	
	Daratumumab	**16mg/kg**	IV infusion		Give via in-line 0.22 micrometre filter. In 500ml Sodium Chloride 0.9% used only if there were no ≥ Grade 1 infusion related reactions (IRR) the previous dose. 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%

TTOs cycle 9 onwards

TTO	Drug	Dose	Route	Directions
	Dexamethasone	4mg	PO	To be taken in the morning for 2 days starting the day after daratumumab treatment.
	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)
	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.
	Consider the use of prophylactic anti-fungals			