Indication	For the treatment of transplant ineligible relapsed multiple myeloma in patients who have received one prior line of treatment. Patients who commenced on the Interim COVID option of ixazomib with lenalidomide and dexamethasone (Blueteq form code IXA2CV) as a second line therapy instead of daratumumab bortezomib and dexamethasone during the COVID19 pandemic to avoid hospital admissions can be granted an exception to the 1 prior line of therapy rule. 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.
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 (except when dexamethasone is given as pre-medication before daratumumab) 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 (due to toxicity). 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	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Consider flu and pneumococcal vaccination pre-therapy. • Monitor FBC on Day 1, 8 and 15 of cycles 1-8, then on day 1 from cycle 9. 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 (see below for guidance on managing neuropathic toxicites) 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. • **<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/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. • **<u>Renal impairment:</u>** o Daratumumab: No dose adjustments necessary. o Bortezomib: CrCl < 20ml/min discuss with consultant. • **<u>Interference with tests (refer to company risk materials):</u>** 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. • **<u>Contraception</u>:** 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. • **<u>Caution with Bortezomib:</u>** o Use with caution in patients with pre-existing heart disease or with high risk factors. o Patients should be advised to report any new or worsening respiratory symptoms. o Bortezomib can affect the ability to drive and use machines. If patients experience fatigue/dizziness or blurred vision they should not drive. • **<u>Drug Interactions:</u>** 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. **<u>Daratumumab infusion rate and infusion related reactions (IRRs)</u>:** • 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.
- **Daratumumab rapid rate infusion**

  The rapid rate of infusion is unlicensed. Patient consent must be obtained.

  Inclusion criteria:
  - Patients on CYCLE 2 onwards and have received and tolerated 500ml daratumumab infusion at the licensed rate (see above) without ≥Grade 1 IRR's.

  Exclusion criteria:
  - Previous ≥grade 3 infusion related toxicity with daratumumab.
  - IRR ≥Grade 1 with the most recent daratumumab infusion given at the standard manufacturer licensed rate.
  - 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.
  - Cardiac amyloid patients.

	Monitoring Parameters for rapid rate infusion: ○ Check vital signs before the start of infusion, then every 15min for the first hour and at the end of the infusion. ○ 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. • 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-038 V4 CDF list V 1.261

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/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: cycle length 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	**CYCLE 1 only:** 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	
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. 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	
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%
	BORTEZOMIB	**1.3mg/m²**	SC	bolus	

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. 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	
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. 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	
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%
	BORTEZOMIB	**1.3mg/m²**	SC	bolus	

TTOs cycle 1-3 only

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	20mg	PO	OM on days 2, 9 and 16.
	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, and then prescribe as required.
	Consider the use of prophylactic anti-fungals			

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	
8	**BORTEZOMIB**	**1.3mg/m²**	SC	bolus	
15	**BORTEZOMIB**	**1.3mg/m²**	SC	bolus	

TTOs cycle 4-8

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	20mg	PO	OM on days 2,8,9,15 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)
	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, and 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
Day 1	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, and then prescribe as required.
	Consider the use of prophylactic anti-fungals			

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

NB: The following pre-medication schedule and administration instructions for daratumumab should be substituted into the main chemotherapy schedule above when rapid infusion daratumumab is used

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%
	*** 20mg for first 2 doses of rapid infusion. Dose can be reduced to 12mg IV/PO from 3rd rapid infusion, applicable to cycle 9 onwards only. Do not reduce dose during cycles 1-8 unless clinically indicated.**				
	NB: For patients with a history of COPD or asthma administer post infusion short and long acting bronchodilators, and inhaled corticosteroids.				