Indication	For the treatment of newly diagnosed and treatment-naive systemic immunoglobulin light chain amyloidosis (AL). NB once daratumumab has been used for this indication and combination it cannot be continued in combination with any other agents and after the completion of up to 24 cycles it will be stopped.
Treatment Intent	Disease modification.
Frequency and number of cycles	Repeat every 28 days. Cycle 1 and 2 weekly daratumumab (total 8 doses). Cycle 3 to 6 2 weekly daratumumab (total 8 doses). Cycle 7 onwards 4 weekly daratumumab. Bortezomib, cyclophosphamide and dexamethasone (except when dexamethasone is given as pre-medication before daratumumab) should be stopped after 6 cycles. Continue daratumumab monotherapy until progressive disease or unacceptable toxicity or patient choice or to a maximum of 24 x 4-weekly cycles of daratumumab counted from the first cycle of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone, whichever occurs first. A formal medical review MUST occur by the end of the first 8 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.
	• 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 clinician's discretion.
	• **Haematological Monitoring:**
	• **Cycle 1 to 6:**
	• Monitor FBC before each cycle and on Day 8 and Day 15 and 22. Proceed when neutrophils >/= 1 x 10^9/L and platelets >/= 50 x 10^9/L.
	• U&Es & LFTs at each cycle.
	• **Cycle 7** onwards: FBC, U&E's & LFTs at each cycle. Proceed when neutrophils > 0.5 x 10^9/L and platelets > 25 x 10^9/L.
	• **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.

- **Renal impairment:**
  - Daratumumab: No dose adjustments necessary.
  - Bortezomib: CrCl < 20ml/min discuss with consultant.
  - Cyclophosphamide: Clinical decision, If GFR > 20 ml/min give 100% dose, if GFR 10 - 20 ml/min give 75% dose and if GFR < 10 ml/min give 50% dose.
- **Dose modification:**
  - 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.
  - 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 or can be adjusted according to tolerability at the clinician's discretion.
  - 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%, (i.e. 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.
  - Cyclophosphamide: if neutrophils <1 or platelets <50 discuss with consultant, consider dose reduction.
- **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.
  - **From cycle 7 only**: If the patient experiences no major IRRs post injection corticosteroids may be discontinued at the clinician's discretion. This ONLY applies to monotherapy.
- **Administration of daratumumab sc:**
  - 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, 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.
- **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 injection.

	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. • **Caution with Bortezomib:** 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 At least 72 hours must elapse between consecutive bortezomib doses. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** o Daratumumab; No interaction studies have been performed. o Bortezomib: 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. o Cyclophosphamide: Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects. Refer to BNF for guidance when administered with other agents. • **Contraception:** To avoid exposure to the foetus, women of reproductive potential should use effective contraception and avoid becoming pregnant during treatment and for 8 months after cessation of bortezomib treatment and 3 months after cessation of daratumumab 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. • **Sodium content:** Each 20ml daratumumab (400mg) contains 1.6mmol sodium. • **Missed dose:** 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. • **Driving**: Patients may experience undesirable effects whilst receiving combination therapy of daratumumab, bortezomib, cyclophosphamide and dexamethasone to include dizziness, blurred vision and visual disturbance patients should be aware of this and not drive or operate machinery if effected. Daratumumab monotherapy should not cause disturbances restricting ability to drive or operate machinery. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Cancerbackup information sheet.
References	KMCC protocol HAEM-MYEL-050 V1 SPC accessed online 24.10.2024

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.	

Cycle 1 and 2 only: 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)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	Montelukast **Cycle 1 only**	10mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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/m²**	SC	bolus	
8	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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/m²**	SC	bolus	
15	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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/m²**	SC	bolus	

Cycle 1 and 2 continued:

Day	Drug	Dose	Route	Infusion Duration	Administration
22	**DEXAMETHASONE**	**20mg**	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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	

TTOs cycle 1 to 6

TTO	Drug	Dose	Route	Directions
Day 1	**DEXAMETHASONE**	**20mg***	PO	Take **20mg** OM on days 1, 2, 8, 9, 15, 16, 22 and 23. (Where appropriate dose must be taken prior to daratumumab Injection) Take with or after food.
	CYCLOPHOSPHAMIDE	**500mg**	PO	OM day 1, 8, 15 and 22. Take with a full glass of water.
	Omeprazole	20mg	PO	OD
	Allopurinol	300mg	PO	OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	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-4mg	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.
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose)
	Aciclovir	400mg	PO	BD
	Pre Med TTO packs to be dispensed.			
	Consider the use of prophylactic anti-fungals			

Cycle 3 to 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)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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	
8	**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)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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	
22	**BORTEZOMIB**	**1.3mg/m^2**	SC	bolus	

Cycle 7 onwards monotherapy
Repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	12mg	PO	stat	To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack)
	Paracetamol	1gm	PO	stat	
	Chlorphenamine	4mg	PO	stat	
	DARATUMUMAB	**1800mg**	SC	bolus	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	Drug	Dose	Route	Directions	
Day 1	Dexamethasone	4mg	PO	To be taken in the morning for 2 days starting the day after daratumumab treatment. NB if no major IRR after sc daratumumab this can be stopped (see notes above)	
	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-4mg	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.	
	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)	
	Consider the use of prophylactic anti-fungals				
	Pre Med TTO packs to be dispensed.				