Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone – D-VCD (Amyloid)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

For newly diagnosed and treatment-naïve patients with systemic immunoglobulin light chain amyloidosis (AL) (NICE TA959)

Response Rates

Phase 3 Andromeda trial:

- CR: D-VCD 53.3% vs VCD 18.1%
- VGPR: D-VCD 78.5% vs VCD 49.2%
- Median time to CR: D-VCD 60 days vs VCD 85 days
- Cardiac response at 6 months: D-VCD 41.5% vs VCD 22.2%
- Renal response at 6 months: D-VCD 53% vs VCD 23.9%

Treatment related mortality: Mayo-stage III patients have an overall mortality risk of 50% in the first year. Patients should be carefully counselled about this very high risk (see 'additional information' section).

Regimen details

Cycle 1-2

Day	Drug	Dose	Route
1, 8, 15, 22	Daratumumab	1800mg	SC
1, 8, 15, 22	Bortezomib	1.3mg/m^2	SC
1, 8, 15, 22	Cyclophosphamide	500mg OD	PO
1, 8, 15, 22	Dexamethasone	20mg OD	PO
2, 9, 16, 23	Dexamethasone	4mg OD	PO

Cycle 3-6

Day	Drug	Dose	Route
1, 15	Daratumumab	1800mg	SC
1, 8, 15, 22	Bortezomib	1.3mg/m^2	SC
1, 8, 15, 22	Cyclophosphamide	500mg OD	PO
1, 8, 15, 22	Dexamethasone	20mg OD	PO
2, 16	Dexamethasone	4mg OD	PO

Cycle 7 onwards

Day	Drug	Dose	Route
1	Daratumumab	1800mg	SC
1	Dexamethasone	20mg OD	PO

Cycle frequency

28 days

Number of cycles

24 cycles

Pre-medication

1-3 hours prior to daratumumab subcutaneous injection:
Paracetamol 500mg-1g PO
Chlorphenamine 4mg PO
Dexamethasone PO – see regimen details above for recommended dosing
Hydration fluids may be required, ensure a fluid intake of at least 3 litres/day on treatment days in cycle 1
Consider montelukast 10mg PO administered >30 mins prior to first dose and subsequent doses in cycle 1

Supportive medication

Cycle 1, Days 1-7: Allopurinol 300 mg OD (100mg OD if CrCl < 20mL/min)
All cycles: Antiviral prophylaxis as per local policy
All cycles: Pneumocystis jirovecii pneumonia (PJP) prophylaxis as per local policy
All cycles: Antifungal prophylaxis as per local policy e.g fluconazole 50mg OD
All cycles: Proton pump inhibitor or H2 antagonist on steroid days or continuously (as per local policy)
Loperamide as required
Bisphosphonates as per SWAG 'Bone Protection Myeloma' protocol

Emetogenicity

This regimen has low emetic potential

Post-infusion medication

For the prevention of delayed infusion reactions to daratumumab, oral corticosteroid (at least 20mg methylprednisolone or equivalent such as 4mg dexamethasone) should be administered on the day after SC injection. This dose can be discontinued from cycle 7 onwards (or sooner if clinically indicated) provided there are no infusion related reactions.

For patients with a history of obstructive pulmonary disorder, the use of post-infusion medications including short- and long-acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four doses, if the patient experiences no major infusion related reactions, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

Administration

Daratumumab

Inject 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 the dose into other sites of the body as no data are available. Injection sites should be rotated for successive injections. The subcutaneous dose 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.

Patients should be observed for at least 6 hours after the end of the SC injection following the first dose (or as per local policy) and, if deemed necessary, after subsequent injections.

Bortezomib

Administration by subcutaneous bolus injection into the thigh or abdomen. Rotate sites, avoid injecting into the same site in the same cycle e.g., alternate between right and left abdomen, and right and left thigh. Avoid site used for daratumumab administration on days when both drugs are administered

Patient should be encouraged to drink 2 – 3 litres over the 24 hours after each dose of bortezomib in the first cycle, to reduce the risk of tumour lysis syndrome. **At least 72 hours must elapse between doses of bortezomib.** If a planned dose of bortezomib is delayed, adjust the dosing schedule accordingly, to maintain the treatment interval.

Cyclophosphamide

Cyclophosphamide is available as 50mg tablets. Tablets should be swallowed whole with a full glass of water. Cyclophosphamide should be taken early in the day and patients encouraged to maintain a good fluid intake. The aim is to reduce the amount of drug remaining in the bladder overnight.

Dexamethasone

Tablets should be taken in the morning, with or immediately after food

Extravasation

Daratumumab is neutral (group 1).
Bortezomib is neutral (group 1).

Mandatory investigations – pre first cycle

Investigation	Validity period
FBC*	14 days
Renal profile (U&Es including creatinine)	14 days
Liver profile (ALT/AST, ALP, bilirubin)	14 days
Virology (Hep B/C, HIV)	3 months

Extended red cell phenotype	Baseline
Pregnancy test (if woman of childbearing potential)	Within 3 days

* If cytopenic prior to initiating treatment, repeat FBC on day 15 of cycle 1. If this is within acceptable limits no additional FBC monitoring is required aside from D1 of future cycles.

Additional investigations advised pre-first cycle

- HBA1C and glucose
- β2 microglobulin
- Serum protein electrophoresis and immunofixation for paraprotein (PP) and immunoglobulins (Igs)
- Serum free light chain (SFLC) assay
- Plasma viscosity
- Bone profile (calcium, phosphate, magnesium)
- CRP
- LDH
- Urine protein/creatinine ratio
- Bone marrow examination for cytogenetic analysis FISH
- Bone marrow aspirate and trephine
- Pulmonary function
- Blood pressure
- Echocardiogram/Cardiac MRIs and ECGs
- NT-proBNP and troponin levels
- Imaging as per local guidelines
- Evaluate for presence of neuropathy prior to starting bortezomib

Investigations – pre subsequent cycles

Investigation	**Validity period**
FBC	7 days
Renal profile (U&Es including creatinine)	7 days
Liver profile (ALT/AST, ALP, bilirubin)	7 days
Pregnancy test (if woman of childbearing potential)	Within 3 days

Additional investigations advised pre subsequent cycles

- SFLC, PP, Igs – results are not required prior to administration of cycle
- Bone profile (calcium, phosphate, magnesium)
- HBA1C and glucose as required
- Blood pressure
- Echocardiogram/Cardiac MRIs and ECGs as required
- NT-proBNP and troponin levels as required
- Clinical assessment of neuropathy with bortezomib

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	≥ 20mL/min
Bilirubin	< 1.5 x ULN

Note: Repeat bloods mid-cycle are not routinely required.

Dose modifications

Bortezomib:

Full dose	1.3mg/m^2
First dose reduction	1.0mg/m^2
Second dose reduction	0.7mg/m^2

Haematological toxicity

To commence a new cycle, platelets should be ≥ 50 x 10^9/L and neutrophils ≥ 1.0 x 10^9/L. If cytopenia considered to be disease related, treatment may be given at consultant discretion.

Daratumumab: no specific modifications or dose reductions are advised. Dose delay maybe considered in grade 3 thrombocytopenia (platelets 25-50 x 10^9/L) with bleeding or grade 4 toxicity (neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L) to allow recovery of blood counts.

Bortezomib: interrupt dosing for grade 4 toxicity (neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L). Bortezomib may be reintroduced at the next dose reduction level once toxicity has resolved (neutrophils > 1.0 x 10^9/L and platelets > 50 x 10^9/L). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Cyclophosphamide:

Toxicity	**Action**
Neutrophils ≥ 1.0 x 10^9/L and Platelets ≥ 50 x 10^9/L	Proceed with full doses
Neutrophils < 1.0 x 10^9/L or Platelets < 50 x 10^9/L (First occurrence)	Delay by 1 week or until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L. Restart at 50% dose when neutrophils and platelets recovered.
Neutrophils < 1.0 x 10^9/L or Platelets < 50 x 10^9/L (Subsequent occurrence)	Omit

Renal impairment

Daratumumab: No dose adjustment necessary.

Bortezomib: No dose modification is required for renal impairment. For dialysis patients, bortezomib should be given after dialysis.

Cyclophosphamide:

CrCl (mL/min)	**Cyclophosphamide dose**
>20	100%
10-20	75%
<10 or requiring dialysis*	50%

*For dialysis patients, dose at a minimum of 12 hours prior to dialysis

Hepatic impairment

Daratumumab: no dose modifications are required in mild or moderate hepatic impairment. Daratumumab has not been studied in severe hepatic impairment – use with caution.

Bortezomib: if bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles consider increasing dose to 1mg/m^2 or reducing dose to 0.5mg/m^2 according to tolerability.

Cyclophosphamide:

Bilirubin (µmol/L)	Cyclophosphamide dose
21-50	100%
51-86	100% - use with caution due to potential reduced efficacy
>86 or Child-Pugh C	Not recommended due to risk of reduced efficacy - discuss with consultant

Other toxicities

Bortezomib:

Neuropathy grade	Bortezomib dose
Grade 1 with no pain or loss of function	100%
Grade 1 with pain or grade 2 but not interfering with daily living	1.0mg/m^2
Grade 2 with pain or grade 3	Withhold until symptoms resolved to ≤ grade 1 or baseline. Restart at 0.7mg/m^2
Grade 4	Discontinue

For any other ≥ grade 3 non-haematological toxicity, withhold bortezomib until recovered to ≤ grade 1 or baseline. Recommence with dose reduction of one level.

Cyclophosphamide: if ≥ grade 2 urinary tract or bladder toxicity, withhold cyclophosphamide and resume once toxicity resolves to ≤ grade 1.

Side Effects

Andromeda study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Lymphopenia	18.7	13
	Neutropenia	10.9	5.2
Non-haematological	Diarrhoea	35.8	5.7
	Peripheral oedema	35.8	3.1
	Constipation	34.2	1.6
	Peripheral sensory neuropathy	31.1	2.6
	Fatigue	26.9	4.1
	Nausea	26.9	1.6
	Upper respiratory tract infection	25.9	0.5
	Hypokalaemia	12.4	1.6
	Pneumonia	10.9	7.8
	Syncope	7.3	5.2
	Cardiac failure	9.3	6.2

Specific drug related side effects:

Daratumumab

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Increased risk of infection	Infusion reaction	Cardiac toxicity
*Hepatitis reactivation	Neutropenia	

*Screening for latent and active viral infections (Hep B, Hep C, HIV) pre-treatment should mitigate this risk. Antivirals should be commenced in the event of positive screening tests

Treatment reactions

Daratumumab can cause severe infusion reactions including anaphylactic reactions. In clinical studies, approximately 8.5% of patients experienced an infusion reaction. Most infusion reactions occurred following the first injection and were grade 1-2. Infusion reactions occurring with subsequent injections were seen in 1% of patients. The median onset of infusion reactions was 3.3 hours. The majority of infusion reactions occurred on the day of treatment. Delayed infusion reactions have occurred in 1% of patients.

Signs and symptoms of infusion reactions may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension and blurred vision. Most common injection site reactions are erythema and rash. Severe adverse reactions include bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma).

Pre-medications must be given at least 1 hour before dosing. Patients receiving SC treatment should be monitored for 6 hours following the first dose (or as per local policy). Monitoring following subsequent SC doses is at the clinician discretion. Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders. If ocular symptoms occur, interrupt daratumumab and seek immediate ophthalmologic evaluation prior to restarting daratumumab.

Bortezomib

Common (>10%)	**Uncommon (1-10%)**	**Rare (<1%)**
Thrombocytopenia, neutropenia, anaemia	Infections	Posterior Reversible Encephalopathy Syndrome
Peripheral sensory neuropathy	Motor neuropathy	Pneumonitis, acute respiratory distress syndrome
Orthostatic hypotension	Rash	Stevens-Johnson syndrome, toxic epidermal necrolysis
Fatigue, asthenia		
Nausea, vomiting		Hepatitis, hepatic failure
Diarrhoea, constipation		Heart failure

Peripheral neuropathy

Patients should be advised to report pain, hypersensitivity, prickling, burning sensation, numbness and paraesthesia. If these occur see above dose reductions for bortezomib and consider use of amitriptyline or gabapentin. Caution in patients with existing peripheral neuropathy.

Dizziness/Orthostatic hypotension

Patients should be advised that bortezomib may cause orthostatic hypotension and they should sit upright for a few minutes prior to standing up from a recumbent position. Caution is advised when treating patients with a history of syncope receiving medications known to be associated with hypotension or in those who are dehydrated. Management of orthostatic hypotension may include adjustment of antihypertensives, rehydration or administration of mineralocorticosteroids and/or sympathomimetics.

Cyclophosphamide

Common (>10%)	**Uncommon (1-10%)**	**Rare (<1%)**
Abnormal hepatic function	Anorexia	Amenorrhoea
Alopecia	Hypersensitivity reaction	Azoospermia/oligospermia
Asthenia	Ovulation disorder	Chest pain
Fever/infection	Pneumonia	Dermatitis/rash
Haematuria	Sepsis	Discolouration of the palms, fingernails, soles
Haemolytic uraemic syndrome		Secondary cancer
Haemorrhagic cystitis		Visual impairment

Impaired spermatogenesis		
Mucosal inflammation		

Dexamethasone

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
*High blood sugars	Blurred vision	Headache
Insomnia	Cataracts	Heart failure
Mood disturbance (depression, anxiety, euphoria)	Osteopenia	
Fluid retention	Acne	
GORD	Abnormal fat deposits	
Increased appetite		

*pre-treatment HBA1C levels should be checked with monitoring for treatment emergent hyperglycaemia when HBA1C levels are >42mmol/mol. Patients with known diabetes/borderline diabetes should be referred to their diabetic nurse for close monitoring upon commencing dexamethasone

Additional information

Daratumumab

Interference with Blood Transfusion Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and may result in a positive Indirect Antiglobulin Test (Coombs test) which may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum with no impact on ABO and Rh blood type.

- The blood transfusion laboratory must be notified that a patient has received daratumumab.
- Patients must have a Blood Group and Antibody screen prior to starting daratumumab.
- Patients require pre-treatment red cell phenotyping/genotyping.
- Ensure patients carry a Patient Alert Card during treatment and for 6 months following discontinuation.
- Counsel patients to inform health care professionals that they received daratumumab, particularly before a transfusion.

Interference with determination of monoclonal protein concentration

Daratumumab is a human IgG kappa monoclonal antibody detectable on serum protein electrophoresis (SPE) and immunofixation (IFE) assays. This interference can impact on the determination of complete response and of disease progression in patients with IgG kappa myeloma.

Dexamethasone dosing

In the Andromeda study, patients received dexamethasone 40mg once weekly. In clinical practice, patients with cardiac and renal amyloidosis commonly demonstrate reduced tolerance to high dose dexamethasone and therefore, the recommended dexamethasone dose used for this protocol is 20mg once weekly. Further dose reductions should be implemented based on individual patient tolerance.

Sudden cardiac death

Amyloidosis with cardiac involvement is commonly stratified according to the Mayo staging system.

Patients with confirmed or suspected cardiac amyloidosis are at increased risk of fatal arrhythmias during the initial days/weeks of therapy. Patient must be appropriately counselled regarding this risk and consideration should be given for telemetry monitoring at treatment initiation.

Telemetry, where clinically indicated, should be arranged on an individual basis in consultation with the trust Cardiology team. Patients requiring monitoring should be admitted to an appropriate cardiology ward to receive at least their first dose of bortezomib. Depending on clinical circumstances, telemetry supported admission may be continued with subsequent doses within the first treatment cycle.

Significant drug interactions – for full details consult product literature/ reference texts

Daratumumab: No interaction studies have been performed.

Bortezomib:
Antihypertensives: Risk of additive hypotensive effect. Close monitoring of blood pressure is required.
Oral antidiabetic agents: Hyper- and hypoglycaemia has been reported. Close monitoring of blood glucose levels is required.
Ciclosporin: increased risk of severe neuropathy - avoid concomitant use.
High dose vitamin C: reduced efficacy of bortezomib - avoid concomitant use.
Cytochrome P34A inhibitors (e.g. itraconazole, voriconazole, posaconazole, clarithromycin, ritonavir) may increase bortezomib levels - avoid concomitant use.
Cytochrome P34A inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) may reduce bortezomib levels - avoid concomitant use.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Carbamazepine: reduced absorption – monitor and adjust dose
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
Valproate: reduced absorption – monitor and adjust dose
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

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Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	17/12/2025	December 2027	New protocol	Written: Dr S Moore (Consultant Haematologist, UHBW NHS Trust) Checked: Anna Wong (Lead Pharmacist for Haematology SACT Protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)