Daratumumab, Lenalidomide & Dexamethasone (DRd) (Myeloma)

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

First line treatment of multiple myeloma when autologous stem cell transplant is unsuitable (NICE TA917)

Response Rates

Phase III MAIA study

- Daratumumab, lenalidomide, dexamethasone (DRd, n= 368) vs lenalidomide dexamethasone (Rd, n= 369)
- ORR: DRd 92.9% vs Rd 81.3%
- PFS: DRd 61.9 months vs 34.4 months. HR 0.55

Regimen details

Cycles 1 & 2

Day	Drug	Dose	Route
1, 8, 15 & 22	Daratumumab	1800mg	SC bolus
1-21 (followed by 7 day break)	Lenalidomide	25mg OD	PO
1, 8, 15 & 22	Dexamethasone	20mg OM*	PO

Cycles 3-6

Day	Drug	Dose	Route
1 & 15	Daratumumab	1800mg	SC bolus
1-21 (followed by 7 day break)	Lenalidomide	25mg OD	PO
1, 8, 15 & 22	Dexamethasone	20mg OM*	PO

Cycle 7 onwards

Day	Drug	Dose	Route
1	Daratumumab	1800mg	SC bolus
1-21 (followed by 7 day break)	Lenalidomide	25mg OD	PO
1, 8, 15 & 22	Dexamethasone	20mg OM*	PO

*Dexamethasone can be increased to 40 mg weekly, in patients <75 years old where rapid disease control is required. On days when daratumumab is administered the dexamethasone dose is given a premedication to the daratumumab.

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity.

Pre-medication

1-3 hours prior to daratumumab subcutaneous injection:
Paracetamol 500mg-1g PO
Chlorphenamine 10mg IV or 4mg PO
Dexamethasone PO – see regimen details above
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)
Cycles 1-3: Levofloxacin 500mg OD (reduced dose if CrCl <50ml/min)
All cycles: Antiviral prophylaxis as per local policy.
All cycles: Proton pump inhibitor or H2 antagonist on steroid days or continuously (as per local policy)
All cycles: Thromboprophylaxis as per local policy.
Consider prophylactic co-trimoxazole if on high dose steroids (>160mg dexamethasone per cycle)
Bisphosphonates as per local policy

Emetogenicity

This regimen has low emetic potential – refer to local policy

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.

Treatment reactions
Daratumumab can cause severe infusion reactions. With SC dosing the incidence of infusion reaction is around 2% with a median onset of 3.5 hours. Severe adverse reactions include bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.
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. 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.

Lenalidomide
Lenalidomide is available in various strengths. Lenalidomide should be swallowed whole with water, either with or without food, at the same time each day and should not be broken, opened or chewed. If a dose is missed it may be taken within 12 hours, however if more than 12 hours has elapsed since the dose was due, the patient should miss the dose and resume the usual dose the next day.

Lenalidomide must be prescribed and dispensed in accordance with the pregnancy prevention programme.

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

Extravasation
N/A

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
- Serum protein electrophoresis
- Serum free light chains
- Immunoglobulins
- β2 microglobulin
- Bone profile (Calcium, phosphate, magnesium)
- CRP
- LDH
- Serum free light chains (SFLC)/Paraprotein (PP)/Immunoglobulins (Igs)
- Urine protein/creatinine ratio
- Bone marrow examination for cytogenetic analysis FISH
- Imaging as per local guidelines

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)

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	≥ 30 x 10^9/L
Creatinine Clearance	≥ 50ml/min
Bilirubin	< 3 x ULN
AST/ALT	≤ ULN

Dose modifications

Lenalidomide

Dose level	Dose
Starting dose	25mg
Dose level -1	15mg
Dose level -2	10mg
Dose level -3	5mg

Haematological toxicity

To commence a new cycle, platelets should be ≥ 30 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 delays maybe considered to allow recovery of blood counts.

Lenalidomide:

Toxicity	Action
Neutrophils <1.0 x 10^9/L	Interrupt lenalidomide treatment, start GCSF and monitor FBC weekly. If first occurrence, restart at same dose once neutrophils ≥ 1.0 x 10^9/L If recurrent neutropenia, restart at one dose level reduction once neutrophils ≥ 1.0 x 10^9/L.
Platelets <30 x 10^9/L	Interrupt lenalidomide treatment and monitor FBC weekly. Once platelet count recovered to ≥ 30 x 10^9/L, restart at one dose level reduction.

Renal impairment

Daratumumab: No dose adjustment necessary.

Lenalidomide:

Creatinine clearance	Lenalidomide dose
> 50ml/min	25mg OD
30-50ml/min	10mg OD
<30ml/min (not requiring dialysis)	15mg alternate days
<30ml/min (requiring dialysis)	5mg OD (on dialysis days, administer after dialysis)

Hepatic impairment

Daratumumab: no dose modifications are required in mild or moderate hepatic impairment (bilirubin ≤3 x ULN or AST/ALT ≤ULN or Child Pugh A or B). Daratumumab has not been studied in severe hepatic impairment (bilirubin > 3 × ULN and any elevation of AST/ALT or Child Pugh C) – use with caution.

Lenalidomide:
Lenalidomide has not been studied in patients with impaired hepatic function and there are no recommendations in terms of dosing.

For management of LFT derangement during treatment:

Bilirubin		**AST/ALT**	**Lenalidomide dose**
≥ 3 x ULN (for ≥5 days)	*or*	AST/ALT ≥ 5 x ULN (for ≥5 days)	Hold until ≤1.5 x ULN. Then resume at next lower dose level
≥ 10 x ULN (any duration)	*or*	AST/ALT ≥ 20 x ULN (any duration)	Hold until ≤1.5 x ULN. Then resume at next lower dose level

Other toxicities

Toxicity	**Definition**	**Dose adjustment**
Neuropathy	Grade 2 with pain or any grade 3	Hold until ≤ grade 2; Resume at reduced dose level.
	Grade 4	Discontinue
Nausea, vomiting, diarrhoea, constipation, dehydration	≥ grade 3	If symptoms persist despite maximal supportive therapy, interrupt lenalidomide until ≤ grade 1 then resume at current dose. For each subsequent event, reduce dose level.
Congestive heart failure	Any symptoms, whether or not drug related.	Interrupt treatment until resolution; After resolution continue treatment at reduced dose level.
Fatigue	≥ grade 3	Interrupt lenalidomide until ≤ grade 1 then resume at current dose. For each subsequent event, reduce dose level.
Rash	Grade 2 or 3	Other causes for rash (e.g. co-trimoxazole) should be ruled out. Treatment of the rash can include topical steroids and emollients, in addition to antihistamines. Interrupt lenalidomide treatment if indicated. If rash resolves resume at next lower dose level.
	Grade 4 or angioedema, anaphylactic reaction, exfoliative or bullous rash, or Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected	Discontinue lenalidomide
Other non-haematological toxicity	≥ grade 3	Interrupt lenalidomide. Assess at least weekly. If toxicity resolves to ≤ grade 1 prior to day 21, resume at reduced dose level and continue the cycle until day 21.

Side Effects

MAIA study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	neutropenia	56.9	50.0
	anaemia	34.6	11.8
	leukopenia	18.7	11.0
	lymphopenia	18.1	15.1
Non-haematological	infections	86.3	32.1
	pneumonia	22.5	13.7
	diarrhoea	56.9	6.6
	constipation	40.9	1.6
	fatigue	40.4	8.0
	peripheral oedema	38.5	1.9
	back pain	33.8	3.0
	asthenia	32.1	4.4
	nausea	31.6	1.4
	secondary primary cancer	8.8	n/a

Treatment related mortality: <5%

Specific drug related side effects:

Lenalidomide:

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Infection	Dry mouth	PML
Bruising or bleeding	Peripheral neuropathy	TLS
Constipation or diarrhoea	VTE	Impotence
Skin rash (see below)	Poor appetite	
Taste changes	Hypothyroidism	
Dizziness/hypotension	Tinnitus	
Bile salt malabsorption (see below)	Loss of appetite/weight loss	
*Teratogenicity	Secondary primary malignancies	

*the pregnancy prevention programme should mitigate this risk

- **Skin rash**

Other causes for rash (e.g. co-trimoxazole) should be ruled out. Treatment of the rash can include topical steroids and emollients, in addition to antihistamines.

- **Bile salt malabsorption**

Bile salt malabsorption (BSM) is a relatively common side effect of lenalidomide therapy and can occur at any time during therapy. It tends to present with symptoms of diarrhoea, urgency and on occasions, incontinence. It is treated with the addition of bile salt sequestrants (e.g. cholestyramine 4g od, colesevelam 1.25-3.75g/day in 2-3 divided doses) with the dose being titrated according to symptoms. Screening for vitamin B12 deficiency is also advised as this can be a recognised complication of BSM.

- **Thrombosis**

If a patient experiences a thromboembolic event treatment with anticoagulation therapy should be initiated and the lenalidomide continued.

- **Pregnancy Prevention**

The conditions of the Lenalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients. All women of childbearing potential must use one effective method of pregnancy prevention at least 4 weeks before therapy, during therapy and for at least 4 weeks after stopping therapy. Men are required to use a barrier method of contraception during treatment.

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

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 disease progression in patients with IgG kappa myeloma.

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

Daratumumab
No interaction studies have been performed.

Lenalidomide
Erythropoietic agents: increased risk of thrombosis – use with caution in patients with high risk to VTE
Hormone treatments (including combined contraceptive pill, HRT): increased risk of thrombosis – use with caution in patients with high risk to VTE
Digoxin: may increase plasma digoxin levels – monitor levels
Statins: increased risk of rhabdomyolysis when statins are administered with lenalidomide

References

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Version	Issue date	Review date	Revision	Written/Checked/Authorised/Amended by:
1	Nov 2023	Nov 2026	New protocol	Written: Dr Sally Moore Checked: Kate Gregory Authorised: Dr Jeremy Braybrooke
1.1	Dec 2023	Nov 2026	CrCl cut off updated to 50ml/min for lenalidomide.	Kate Gregory
1.2	April 2024	Nov 2026	Reformat of protocol template.	Kate Gregory