DVd Protocol

Daratumumab (Darzalex®) + Velcade® (bortezomib) + Dexamethasone (including split dose option for first dose of daratumumab and rapid infusion option from cycle 2 day 1 - i.e. fourth dose - onwards)

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INDICATION: DVd is indicated as an option for treating relapsed myeloma in patients who have had 1 previous treatment and who have not been refractory to Velcade® (bortezomib) first line.

Prior to consent

- Patients must have an ECOG performance status of 0, 1 or 2
- Patients must have evidence of relapse or progressive myeloma as defined by IMWG criteria (see appendix 1 below)
- Check PFTs if the patient has a history of airways disease within the last 2 years. If they have COPD, their FEV1 must be 50% of predicted normal or greater, and if they have persistent asthma it must be mild.
- Patients must not have clinically significant cardiac disease. Check hepatitis B and C screen – there is a reactivation risk associated with daratumumab use.
- Because CD38 is weakly expressed on human erythrocytes, daratumumab can interfere with antibody screening and cross-matching, though ABO/RhD typing is not usually affected. Once the patient has consented to therapy, **the blood transfusion laboratory must be informed.** Prior to commencing daratumuab take 2 separate transfusion samples at least 15 minutes apart for grouping and local testing if the patient has not been previously grouped and also a further 2 transfusion sample tubes for analysis at NHSBT. Patient plasma can remain pan-reactive for 2 - 6 months after the last daratumumab infusion.
- Consider use of erythropoietin, particularly in anaemic patients with renal impairment

Prior to each cycle

- The first daratumumab infusion must be administered as an inpatient unless the split dose regimen is being used in view of the length of time required to complete. If tolerance is good, day 8 of cycle 1 and subsequent infusions can be given on a haematology day unit.
- Check that transfusion laboratory are aware of the patient as above.
- Women of childbearing potential must have a negative pregnancy test at screening and men who are sexually active with a woman of childbearing potential must agree to use barrier methods of contraception
- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Check FBC, U&Es and LFTs including ALT. Discuss with consultant if significant cytopenia or if renal or hepatic function have changed significantly.
- Lab exclusions include neutrophils < 0.5, Hb < 70, platelets < 50, ALT > 2.5 times normal.
- Daratumumab, bortezomib and dexamethasone can all be used safely in renal failure but if the creatinine clearance is < 30 inform consultant (see dose modification notes below also)
- HMDS must be informed that the patient is on daratumumab on any sample request forms sent to them, as the presence of the antibody can interfere with identification of plasma cells for flow cytometry
- As daratumumab is an IgG k monoclonal it can co-migrate with IgG k paraproteins on serum electrophoresis making identification of CR difficult - consider DIRA assay if available in discussion with biochemistry

DVd		
Daratumumab	**16 mg/Kg***	IV day 1, 8, 15 (i.e. weekly) for cycle 1, 2 and 3 then day 1 (i.e. every 21 days) for cycle 4 - 8 then as a single agent every 28 days from cycle 9 until progression
Velcade (bortezomib)	**1.3 mg/m^2**	s/c day 1, 4, 8 and 11 cycles 1 to 8
Dexamethasone	**20 mg**	oral (**or IV – see daratumumab pre-medication instructions below**) day 1 & 2, 4 & 5, 8 & 9, 11 & 12 cycles 1 to 8 [also day15 & 16 in cycle 1-3 only] (the dose can be reduce to 20 mg weekly for patients > 75 yrs or BMI < 18.5. **Note: If a weekly dose is used it must be given pre-daratumumab so it can act also as a daratumumab pre-medication)** **Cycles 1 to 8 occur every 21 days** **Cycle 9 and subsequent cycles occur every 28 days**

***If using split dosing for 1st dose give 8 mg/Kg day 1 and then repeat on day 2 (see below also). A cycle is defined as 28 days (4 weeks). Rapid infusion over 90 minutes from cycle 2 is not licensed but there is good evidence of its safety in the absence of > grade 1 infusion-related reactions during cycle 1. Patients must be consented for rapid rate infusion appropriately and consultant must take responsibility.**

- Continue therapy until relapse or unacceptable toxicity. Continue for stable disease.
- First infusion (day 1, cycle 1) – can be given in single dose infusion or split dose on two consecutive days. Due to the time it takes to give the first dose as a single infusion a ward environment is required as infusions times are likely to continue past 5pm. Daratumumab can however be given as a split dose on two consecutive days to allow day unit administration. For a single dose infusion daratumumab is diluted in **1 litre** of normal saline – initial rate **50ml/hour**, escalating by an additional 50ml/hour every 60 minutes if well tolerated during the first 3 hours to a max rate of 200ml/hour. For split dose infusions on consecutive days daratumumab should be given at a dose of 8mg/Kg in 500ml of normal saline day 1 and then again on day 2 at an initial rate of 50 ml/hour
- Infusion 2 (day 8, cycle 1) – if there was an infusion-related reaction within 1st 3 hours of first dose consult SPC, otherwise daratumumab is diluted in **500ml** of normal saline – initial rate **50 ml/hour** escalating by an additional 50ml/hour every 60 minutes if well tolerated during the first 3 hours to a max rate of 200 ml/hour.
- Infusion 3 (day 15, cycle 1) and subsequent infusions – daratumumab is diluted in **500ml** of normal saline – initial rate **100 ml/hour** escalating by an additional 50 ml/hour every 60 minutesif well tolerated during the first 3 hours to a max rate of 200 ml/hour

	Dilution volume	**Initial rate (first hour)**	**Rate increment**	**Maximum rate**	**Location**
First infusion single dose	1000 ml (16mg/Kg daratumumab dose)	50 ml / hour	50 ml / hour every hour	200 ml / hour	Inpatient Ward
First infusion split dose day 1 and repeat day 2	500 ml (8mg/Kg daratumumab dose)	50ml / hour	50 ml / hour every hour	200 ml / hour	DCU
Second infusion	500 ml (16mg/Kg daratumumab dose)	50 ml / hour	50 ml / hour every hour	200 ml / hour	DCU
Third and Fourth infusions (i.e. to complete cycle 1)	500 ml (16 mg/Kg daratumumab dose)	100 ml / hour	50 ml / hour every hour	200 ml / hour	DCU
Cycle 2 onwards (i.e. fifth infusion onwards) if tolerated well in cycle 1 then use rapid infusion	500 ml (16 mg/Kg daratumumab dose)	Infuse the first 100ml over 30 minutes and then the remaining 400ml over 1 hour (total infusion time = 90 minutes)			DCU

- Check full observations every 15 minutes during the first hour of day 1 cycle 1 and then hourly until completion.
- Once out of the fridge, the first daratumumab infusion should be completed within 15 hours.

Pre-daratumumab infusion medications (approx. 1 hour prior)	Paracetamol 1G oral, Chlorphenamine 10mg IV, Dexamethasone 20mg (use IV dexamethasone prior to first daratumumab infusion but then use oral subsequently). **(Note: on daratumumab weeks during cycles 1 to 8 the pre- and post daratumumab infusion dexamethasone is also being used as the steroid component of the triple combination regime.)** For the <u>first</u> rapid rate daratumumab infusion however, the 20 mg dexamethasone dose should be given IV again and 10mg oral montelukast also given. From cycle 9 onwards when daratumumab is used as a single agent every 28 days, the dexamethasone pre-med dose can be reduced to 12 mg oral.
Post-daratumumab infusion medications	For cycles 1 to 8 the second day of dexamethasone 20mg oral acts as the post-daratumumab infusion medication as well as the steroid component of the triple drug combination. For cycle 9 onwards, when daratumumab is used as a single agent, reduce dexamethasone dose to 8mg oral the day following the daratumumab infusion. For patients with high risk for respiratory complications (e.g. FEV1 between 50% and 75% of predicted), consider also adding an antihistamine, short acting β2 receptor agonist such as salbutamol and inhaled steroid for 2 days following daratumumab.
Other medications	Allopurinol 300mg od for 7 days (100mg if Cr.Cl <20ml/min) for cycle 1, acyclovir 400mg BD prophylaxis throughout

DaratumumabToxicities

Daratumumab is a monoclonal antibody directed against CD38, an antigen found on the surface of plasma cells. Many of its side effects are therefore similar to other monoclonal antibody therapies such as rituximab, with 50% of patients suffering infusional reactions including flushing, pyrexia, sweats, and dyspnoea. Unlike rituximab, however, daratumumab can also be associated with upper respiratory tract symptoms such as cough, allergic rhinitis nasal congestion and throat irritation, which patients should be warned about in advance to help prepare them for what can be an alarming side effect. Similar to other monoclonal antibodies however, all side effects tend to completely settle after the first infusion, such that subsequent infusions are usually well tolerated.

Pyrexia	Cough , choking sensation,	Throat irritation
Sweats	Nasal congestion	
Fatigue	Allergic rhinitis,	
Dyspnoea, wheeze	Diarrhoea	
Cytopenias	Hypertension	

Bortezomib Toxicities

Thrombocytopenia	Nausea
Neutropenic sepsis	Fatigue
Fluid retention & cardiac failure	Diarrhoea, constipation & ileus
Peripheral neuropathy (may be painful)	Hypotension
Fatigue, malaise, weakness	

Bortezomib Dose modification for neutropenia (unless due to disease)

• Neutrophils <0.5 or platelets <25 on day 1 of cycle	Stop until > 1.0 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** GCSF prophylaxis
• No resolution of neutropenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modification for thrombocytopenia (unless due to disease)

• Platelets <25 on day 1 of cycle	Stop until >25 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** Support with platelet transfusion
• No resolution of thrombocytopenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modifications for peripheral neuropathy

• Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function	No change
• Grade 1 with pain or Grade 2, i.e objective sensory loss or paraesthesia interfering with function but not activities of daily living	Reduce to 1.0mg/m^2
• Grade 2 with pain or Grade 3, i.e sensory loss or paraesthesia interfering with activities of daily living	Withhold until symptoms resolve, then restart at 0.7mg/m^2 at once a week. If symptoms fail to resolve within 2 weeks – stop treatment
• Grade 4, i.e permanent sensory loss that interferes with function	Discontinue bortezomib

Modification for renal dysfunction

- If creatinine clearance < 30ml/min *discuss with consultant*. Note that the incidence of serious adverse effects increases with mild-moderate renal impairment. Patients have been treated safely when the creatinine clearance is <30ml/min and on dialysis but monitor carefully for toxicities if renal function is impaired.

Modification for liver dysfunction

- The major route of bortezomib excretion is hepatic and there is limited on the use of bortezomib in patients with hepatic impairment. If bilirubin >30μmol/L use with caution, monitor closely for toxicity and consider dose reduction – *discuss with consultant*

Dose modification for diarrhoea

• If ≥ grade 3 diarrhoea, i.e increase of ≥ 7 stools/day over baseline, incontinence, hospitalization with >24 hrs IV fluids	Reduce dose to 1.0mg/m^2, then 0.7mg/m^2 if symptoms persist

Appendix 1:

International Myeloma Working Group Criteria for progressive disease requires an increase of ≥ 25% from the lowest response value in any one or more of the following:

1. Serum M-component (the absolute increase must be ≥ 5 g/L)
2. Urine M-component (the absolute increase must be ≥ 200 mg/24hrs)
3. Involved serum free light chain level increase of ≥ 200mg/L in 2 consecutive measurements separated by ≤ 2 months (plus an abnormal FLC ratio)
4. Bone marrow plasma cell percentage (the absolute percentage must be ≥ 10%)
5. Development of new soft tissue plasmacytoma or bone lesions
6. Hypercalcaemia > 2.65 mmol/L

International Myeloma Working Group Criteria for relapse requires one or more of the following:

1. Development of new soft tissue plasmacytoma or bone lesions
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcaemia > 2.65 mmol/L
4. Decrease in Hb of ≥ 20 g/L
5. Rise in serum creatinine to ≥ 177 mmol/L
6. Hyperviscosity

References:

- MMY3004/CASTOR: Phase III Study comparing DVd with Vd among patients with RMM. Daratumumab, Bortezomb and Dexamethasone for Multiple Myeloma. Palumbo et al, N Engl J Med 2016; 375: 754-66.
- Resolving the daratumumab interference with blood compatability testing. Chapuy C I et al, Transfusion 2015; 55 (6 Pt 2): 1545 – 1554.
- Consensus Recommendations for the uniform reporting of clinical trials: report of the international myeloma workshop consensus panel 1. Rajkumar et al, Blood, May 5, 2011, vol 117 no18 p 4691 – 4695.
- Ninety-minute daratumumab infusion is safe in multiple myeloma. Barr H et al. Blood 2017 130: 1889.

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