SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

DVd - DARATUMUMAB (SUBCUTANEOUS), BORTEZOMIB & DEXAMETHASONE MYELOMA

PROTOCOL REF: MPHASCDVDHA
(Version No. 1.1)

Approved for use in:

Daratumumab in combination with bortezomib and dexamethasone is approved for use in relapsed/refractory multiple myeloma when the following conditions have been met:

- Patient has received and responded to 1, and no more than 1 prior line of treatment **(i.e. 2nd line treatment only)** and now relapsed and are ineligible for transplant.
- Daratumumab only to be used in combination with bortezomib and dexamethasone, and with no other agents, as per licensing.
- If the patient has previously been treated with daratumumab, they must have received and responded to it as part of induction therapy pre-transplant. Otherwise they must not have previously received daratumumab or an anti-CD38 antibody (isatuximab). ***i.e daratumumab may have been used previously as part of D-VTD at 1st line in the transplant eligible setting.***
- Daratumumab is not routinely funded for amyloidosis.

Blueteq registration must be completed prior to initiation

Dosage:

Patients should start with the licensed twice-weekly dose of bortezomib. However, where twice weekly schedule is not appropriate consideration should be given to using a weekly schedule at consultant's discretion

Twice weekly bortezomib (cycles 1 to 8):

Drug	Dosage	Route	Frequency
Cycle 1 to 3			
Daratumumab	1800mg	S/C	Days 1, 8, 15
Bortezomib	1.3mg/m^2	SC	Days 1, 4, 8 and 11
Dexamethasone	20mg	PO	Days 1, 2, 4, 5, 8, 9, 11, 12, 15 and 16
Cycles 4 to 8			
Daratumumab	1800mg	S/C	Day 1
Bortezomib	1.3mg/m^2	SC	Days 1, 4, 8 and 11
Dexamethasone	20mg	PO	Days 1, 2, 4, 5, 8, 9, 11 and 12
Cycle 9 onwards – see below			

Once Weekly bortezomib (cycles 1 to 8)

Drug	Dosage	Route	Frequency
Cycle 1 to 3			
Daratumumab	1800mg	S/C	Days 1, 8, 15
Bortezomib	1.3mg/m^2	SC	Days 1, 8, 15
Dexamethasone	20mg	PO	Days 1, 2, 8, 9, 15 and 16
Cycles 4 to 8			
Daratumumab	1800mg	S/C	Day 1
Bortezomib	1.3mg/m^2	SC	Days 1, 8 and 15
Dexamethasone	20mg	PO	Days 1, 2, 8, 9, 15 and 16
Cycle 9 onwards – see below			

Cycle length every 21 days (3 weeks) from cycle 1 to 8.

Cycle 9 onwards:

Drug	Dosage	Route	Frequency
Cycle 9 onwards			
Daratumumab	1800mg	SC	Day 1
Dexamethasone	12mg	PO	Day 1
Dexamethasone	4mg	PO	Days 2 and 3*

*May be discontinued if no Infusion Related Reactions

Cycle length every 28 days (4 weeks) from cycle 9 onwards. Continue until disease progression or unacceptable toxicity.

Administration / counselling:

- **Due to the risk of injection-related reactions (IRRs), pre-medications should be administered approximately 1 to 3 hours before each daratumumab injection.**
- Dexamethasone used in cycles 1 to 8 is being used as both chemotherapy agent and also to prevent delayed daratumumab IRRs - counsel patients on the importance of these. In the absence of IRRs post-infusion dexamethasone can be stopped from cycle 9 onwards.
- Daratumumab interferes with indirect antiglobulin test (**indirect Coombs test**). Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test, which may persist for up to 6 months after the last daratumumab administration. Patients should be typed and screened prior to starting daratumumab. Phenotyping should be undertaken prior to commencing treatment as per local practice. In the event of a planned transfusion, blood transfusion centres should be notified of this interference with indirect antiglobulin tests. See SPC for further details.
- At least 72 hours should elapse between administrations of bortezomib.
- Blood transfusion requirements – alert card
- Contraceptive advice – male and female of childbearing potential must use effective contraceptive measures during and for 3 months following treatment.

Ward Based Handling of Daratumumab Vials

- Daratumumab solution for injection should be given by subcutaneous injection only, using the dose specified. Single-use vial, fixed dose of 1800mg daratumumab.
- Once drawn up into the syringe, it must be administered within 4hours
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous injection set to the syringe immediately prior to injection.
- Inject 15 mL daratumumab solution for subcutaneous injection 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 daratumumab solution for subcutaneous injection 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 medications medicinal products for subcutaneous use at the same site as daratumumab.
- Do not use if opaque particles, discoloration or any other foreign particles are visibly present in the solution.

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Daratumumab pre-injection medications

To be administered at least 1 hour prior to daratumumab injection:

- Montelukast 10mg oral STAT (prior to cycle 1 only but continue if COPD/Asthma)
- Paracetamol 1000mg oral STAT

- Chlorphenamine 4mg oral STAT
- Dexamethasone oral STAT (dose dependant on stage of therapy)

Supportive medications

- Allopurinol PO 300mg daily (cycle 1 only)
- Aciclovir PO 400mg twice daily for the duration of the treatment and for 3-6 months after
- Co-trimoxazole PO 480mg daily for the duration of treatment and for 3-6 months after
- Dexamethasone oral 4mg once daily on the 2 days following daratumumab (cycle 9 onwards) to prevent post injection related reactions (IRRs). Can be stopped if no major IRRs.
- Omeprazole 20mg once daily (consider stopping from cycle 9)
- Nystatin oral suspension 1mL QDS or Fluconazole PO 50mg once daily as indicated (not needed routinely)

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medications including short/long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major injection related reactions (IRRs), these inhaled post-injection medications may be discontinued at clinician discretion.

Extravasation risk:

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal Dose Modifications	
Daratumumab	No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment.
Bortezomib	No dose reductions necessary if eGFR >20ml/min Unknown PK data in patients with severe renal impairment not undergoing dialysis Dialysis may reduce bortezomib concentrations and therefore should be administered after dialysis

Hepatic Dose Modifications		
Daratumumab	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment.	
Bortezomib	**Bilirubin (µmol/L)**	**Modification**
	>1.5 x ULN	Reduce bortezomib to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability

Interactions:

Daratumumab – No known drug interactions

Bortezomib - Patients on bortezomib should be closely monitored if on a potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir), or a strong CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's wort).

Please refer to the SPC for full list of interactions and further information.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
Cycle 1 to 3				
1	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone	**20mg**	**Oral**	
	Montelukast*	**10mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
	Bortezomib	**1.3mg/m^2**	**SC**	Over 3-5 minutes
	Dexamethasone	**20mg**	**Oral**	TTO: Once daily on days 2, 5, 9, 12 and 16
4	**Dexamethasone**	**20mg**	**Oral**	
	Bortezomib	**1.3mg/m^2**	**SC**	Over 3-5 minutes **(omit if weekly regimen used)**
8	**As per Day 1**			
11	**Dexamethasone**	**20mg**	**Oral**	
	Bortezomib	**1.3mg/m^2**	**SC**	Over 3-5 minutes **(omit if weekly regimen used)**
15	**As per Day 1**			

Cycle 4 to 8				
1	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone	**20mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
	Bortezomib	**1.3mg/m^2**	**SC**	Over 3-5 minutes
	Dexamethasone	**20mg**	**Oral**	Once daily on days 2, 5, 9, and 12
4, 8, 11	**Dexamethasone**	**20mg**	**Oral**	
	Bortezomib	**1.3mg/m^2**	**SC**	Over 3-5 minutes **(omit day 4 and 11 if weekly regimen used)**
15	**Bortezomib**	**1.3mg/m^2**	**SC**	Over 3-5 minutes **(ONLY TO BE USED IN WEEKLY REGIMEN)**
Cycle 9 onwards				
1	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone	**12mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
	Dexamethasone**	**4mg**	**Oral**	Once daily on days 2, 3 only if needed for IRRs

*Montelukast should be continued as a pre-med if history of asthma/ COPD

**Post injection steroids can stop after the third dose if no IRRs

Main toxicities:

Daratumumab
Neutropenia, thrombocytopenia, anaemia, hepatotoxicity, headache, nausea, diarrhoea, constipation, vomiting, dyspepsia, abdominal pain, fluid retention, dermatitis, muscle spasm and cramps, musculoskeletal pain. Reactivation of HBV has also been reported. Infection (pneumonia, bronchitis), reduced appetite, hypogammaglobulinaemia, hyperglycaemia, hypocalcaemia, insomnia, peripheral neuropathy, atrial fibrillation, hypertension, fatigue.
Bortezomib
Serious adverse reactions uncommonly reported during treatment with bortezomib include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy. The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Investigations and treatment plan:

	Pre	Cycle 1	Before each dose of daratumumab	Before each dose of bortezomib	Cycle 2	Cycle 3 onwards	Ongoing
Informed Consent	X						
Clinical Assessment inc toxicity review + PS	X	X			X	X	Prior to every cycle
OTR and SACT Assessment	X	X	X	X	X	X	Prior to every dose
Blood pressure/ Pulse/ Temperature/ Respiratory rate			X				See injection related reactions section on page 12 for further information
FBC, U&E and LFTs, bone profile	X	X			X	X	Prior to every cycle
CrCl	X	X			X	X	Prior to every cycle
HbA1C	X						Repeat as clinically indicated
B2Microglobulin	X						
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X			X	X	Prior to every cycle
Red cell phenotype (notify transfusion lab)	X						
Hepatitis B/C serology	X						
Pregnancy test	X						As clinically indicated
Neurological assessment (for neuropathy)	X	X			X	X	
Height recorded	X						
Weight recorded	X	X			X	X	Prior to every cycle
Imaging as per NICE/network guidance and clinical indication	X						To restage as indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle can occur if:

ANC ≥ 0.5 x10^9/L	Platelets ≥ 25 x 10^9/L

Neutrophils (x10^9/L)	Platelets (x10^9/L)	Action
<0.5	<25x10^9/L	Delay bortezomib on a weekly basis, until recovery of toxicity, then reinitiate at 25% reduced dose (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0mg/m^2 reduced to 0.7mg/m^2) If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Daratumumab delay may be required to allow recovery of blood cell counts. No dose reduction of Daratumumab is recommended. Consider supportive care with transfusions or growth factors.

Non- Haematological toxicity:

See section 'Dose modifications for Renal and Hepatic Impairment'

Neuropathy (Bortezomib):

Grading of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or Change treatment schedule to 1.3 mg/m^2 once per week
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Injection-related reactions:

Injection-related reactions (IRRs) can happen when daratumumab is administered. Monitor patients throughout the injection and the post-injection period (especially during the first and second injections). The following monitoring requirements schedule should be followed;

First Injection
Monitor patient for 4 hours post infusion including blood pressure, pulse, temperature and respiratory rate pre-injection and every 30 minutes thereafter
Second and subsequent Injection
There is no need to routinely monitor blood pressure, pulse, temperature and respiratory rate. Keep patients for 30 minutes after injection, can be sent home if feel well. **Note patients should be kept for longer if they experienced a grade 2+ IRR during their previous injection.** Severe reactions can occur, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms noted predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension. Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab. 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. Medical management/supportive treatment for IRRs should be instituted as needed. Daratumumab therapy should be permanently discontinued in the event of life-threatening IRRs.

References:

1. https://www.medicines.org.uk/emc Daratumumab
2. National Institute for Health and Care Excellence (April 2019). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma [TA573]
3. Summary of Product Characteristics, Darzalex®, Daratumumab, Janssen-Cilag Ltd. Updated May 2023, http://www.medicines.org [accessed on June 2023]
4. Summary of Product Characteristics, Velcade® Bortezomib, Janssen-Cilag Ltd. Updated Jan 2022. http://www.medicines.org.uk [accessed June 2023]
5. Antonio Palumbo, M.D *et al*. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med 2016; 375:754-766*
6. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08

Circulation/Dissemination

Date added into Q-Pulse	13th October 2023
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
June 2020	1.0	**Niamh Mclaughlin – HO Pharmacist**	**New protocol**
July 2023	1.1	**Jennifer Gibson – Principal HO Pharmacist**	**Three yearly review. New template. Updated indications. Removed COVID measure.**