SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

DARATUMUMAB (SUBCUTANEOUS) MONOTHERAPY MYELOMA

PROTOCOL REF: MPHASDAMHA
(Version No. 1.1)

Approved For Use In:

Daratumumab monotherapy is approved for use in relapsed/refractory multiple myeloma when the following conditions have been met:

- Patient has received 3 and no more than 3 prior lines of treatment (**i.e. 4th line treatment only**). Please note induction chemotherapy and stem cell transplantation is considered to be 1 line of therapy.
- Patient must have been previously treated with a proteasome inhibitor (bortezimib/ carfilzomib/ ixazomib) and an immunomodulatory agent (thalidomide / lenalidomide)
- 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, but not part of DVD at 2nd line.***
- Daratumumab is not routinely funded for amyloidosis.

Blueteq registration must be completed prior to initiation

Dosage:

Drug	Dosage	Route	Frequency
Cycle 1 and 2			
Daratumumab	1800mg	S/C	Weekly on days 1, 8, 15 and 22
Cycles 3-6			
Daratumumab	1800mg	S/C	Every two weeks (starting week 9) On days 1 and 15
Cycle 7 onwards			
Daratumumab	1800mg	S/C	Every four weeks (starting week 25) on day 1

Cycle length: 28 days. 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 3hours before each daratumumab injection.**
- Steroids are given for 2 days after treatment to prevent delayed IRRs – counsel patients on the importance of these. In the absence of IRRs following the first 3 injections, the post-dose steroids can be stopped.
- Daratumumab interfers 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 before treatment begins 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.
- 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:

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 300mg PO daily for 28 days (cycle 1 only)
- Aciclovir 400mg PO twice daily for the duration of the treatment and for 3-6 months after
- Co-trimoxazole 480mg PO daily for the duration of treatment and for 3-6 months after
- Dexamethasone oral 4mg once daily on the 2 days following daratumumab to prevent post injection related reactions (IRRs). Can be stopped if no major IRRs after the third dose.
- Omeprazole 20mg PO once daily (first two cycles, review ongoing need after this)
- Nystatin 1ml QDS oral suspension or Fluconazole 50mg PO 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.

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.

Interactions:

No known drug interactions.

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

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
Cycle 1				
1, 8, 15,22	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone	**20mg**	**Oral**	
	Montelukast*	**10mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
	Dexamethasone**	**4mg**	**Oral**	Once daily on days 2, 3, 9, 10, 16, 17 then stop if no IRR
Cycle 2				
1, 8, 15, 22	**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, 9, 10, 16, 17, 23 &24 only if needed for IRRs
Cycle 3 to 6				
1 and 15	**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, 16 and 17 only if needed for IRRs
Cycle 7 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.

Investigations and treatment plan:

	Pre	Cycle 1	Prior to each dose	Cycle 2	Cycle 3 onwards	Ongoing
Informed Consent	X					
Clinical Assessment inc toxicity review + PS	X	X		X	X	Prior to every cycle
On treatment review and SACT assessment			X			Prior to each dose
Blood pressure/ Pulse/ Temperature/ Respiratory rate			X			See IRR information
FBC	X	X		X	X	Prior to every cycle
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					
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:

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'

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 injection including blood pressure, pulse, temperature and respiratory rate pre-injection and every 30 minutes thereafter
Second and subsequent Injections
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 with their previous injections.** 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 2022). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma [TA783]
3. Summary of Product Characteristics, Darzalex®, Daratumumab, Janssen-Cilag Ltd. May 2023, http://www.medicines.org [accessed on June 2023]
4. 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

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Version History

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