Daratumumab (Darzalex®) single agent via subcutaneous route NICE TA510 March 2018. Subcutaneous licence June 2020.

INDICATION: Patients with relapsed / refractory myeloma who have received 3 lines of prior therapy including a proteasome inhibitor (PI, e.g. bortezomib) and an immunomodulatory agent (IMiD, e.g. thalidomide, lenalidomide). For use within the cancer drugs fund. Daratumumab cannot be used before or after 4th line.

Prior to commencing

- Patients should have an ECOG performance status of 0, 1 or 2 and no significant cardiac problem.
- Patients must have evidence of relapse or progressive myeloma on or after the most recent treatment regime as defined by IMWG criteria as in appendix 1.
- 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 have received 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent and not received daratumumab or other anti-CD38 antibody previously

Immediately after consent obtained

- 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
- Subcutaneous Daratumumab does not have established efficacy in patients weighing over **120kg**.

Prior to each cycle

- The first dose on day 1 of cycle 1 can be administered on haematology day unit
- Check that transfusion laboratory staff 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 immunotherapy – 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.
- Renal failure does not affect the pharmacokinetics of monoclonal antibodies like daratumumab but if the creatinine clearance is < 20 ml/min this is an exclusion for the trial
- 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 - DIRA assay is available in this trial which removes dara in the sample

s/c Daratumumab	**1800 mg (i.e. fixed dose)**	s/c	days 1, 8, 15, 22 (i.e. weekly) for cycle 1 and 2
(daratumumab with rHuPH20 -		then	days 1 and 15 (i.e. fortnightly) for cycle 3,4,5 and 6
recombinant human hyaluronidase)		then	day 1 only (i.e. monthly) for cycle 7 and subsequently

The s/c vial volume is 15 ml and the dose is given as a manual push over 3 – 5 minutes in the abdominal s/c tissue alternating sides between individual doses. Reactions to the subcutaneous route are much rarer than the IV route at only 7% of cases, typically occurring with the first injection and grade 1 or 2 only. Check full observations after the end of the s/c injection during cycle 1 day 1 every 15 minutes during the first hour. If the patient remains well they can then be discharged. Tolerance of the first injection means subsequent injections are tolerated well. Continue therapy until relapse, unacceptable toxicity or end of study. Continue for stable disease

Pre-dose medications **(approx. 1 hour prior)**	Paracetamol 1 gram oral, chlorpheniramine 4 mg oral and Dexamethasone 20 mg oral should be given 1hour prior to Daratumumab. If no IRRs following first 2 doses, subsequent dexamethasone dose pre-daratumumab can be reduced to 12mg.
Post-dose medications	Dexamethasone 4mg od for 2 days following each Daratumumab dose. Aciclovir 400mg po bd continuous prophylaxis 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.

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	

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:

- Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label randomized phase 2 trial. Lonial et al, The Lancet, 06 Jan 2016.
- 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.
- MMY1004 Phase 1b Study Review of s/c daratumumab safety and tolerability
- Columba Trial Study Protocol
- SPC Darzalex 1800mg solution for injection SPC accessed 22/06/2020

Written by	Dr Mark Grey, Consultant Haematologist
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