Thames Valley
Strategic Clinical Network

DARATUMUMAB MONOTHERAPY

INDICATION

Relapsed/refractory multiple myeloma in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent and who have demonstrated disease progression/refractoriness with the last therapy.

This regime is funded via **CDF interim Funding.** Requires **Blueteq** Application

Subcutaneous daratumumab is the standard of care.

Intravenous administration remains an option in very selected clinical situations at the clinician discretion (Refer to Appendix 1).

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&E
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology: EBV, CMV, Hep B, Hep C, HIV serology
   - Consider annual flu and pneumococcal vaccination pre therapy
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions. Samples should be sent to

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospita
Salisbury
Wiltshire, SP2 8BJ

   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - **Send a "group and save" sample to transfusion and inform patient and transfusion**

laboratory that patient is due to commence Daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of Daratumumab to red cells.
- Imaging as per NICE/network guidance and clinical presentation

Additional Investigations
- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

2. Counselling about risks in pregnancy - There are no human data to inform a risk with use of daratumumab during pregnancy. However, Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta after the first trimester of pregnancy.. Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.
3. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight, dose on actual body weight.
7. Document patient's performance status.
8. Treatment must be agreed at the relevant MDT.

REGIMENSPECIFIC PRE-ASSESMENT

1. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.
2. Advise patients to inform their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.

METHOD OF SUBCUTANEOUS DARATUMUMAB ADMINISTRATION:

Inject the subcutaneous dose (15 mL) 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 at 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.

DRUG REGIMEN

Cycles 1 &2

Pre-meds	Paracetamol 1g PO, Montelukast 10mg PO on **(cycle 1 only)**, Chlorphenamine 4mg PO Dexamethasone 20mg PO (can be reduced to 12mg PO following the second injection)	To be given 1 hour prior to daratumumab injection
Daratumumab	Subcutaneously at 1800mg fixed dose over 3-5 minutes	Days 1, 8, 15 and 22
Post-daratumumab	Dexamethasone 4mg PO	Days 2, 3, 9, 10, 16, 17 and 23, 24 i.e. for two days starting the day after daratumumab to reduce the risk of delayed reactions

Cycles 3 to 6

Pre-meds	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO	To be given 1 hour prior to daratumumab injection
Daratumumab	Subcutaneously at 1800mg fixed dose over 3-5 minutes	Days 1 and 15
Post-daratumumab	Dexamethasone 4mg PO	Days 2,3 and 16,17 i.e. for two days starting the day after daratumumab injection to reduce the risk of delayed reactions

Cycle 7- Onwards

Pre-meds	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO	To be given 1 hour prior to daratumumab injection
Daratumumab	Subcutaneously at 1800mg fixed dose over 3-5 minutes	Days 1
Post-daratumumab	Dexamethasone 4mg PO	Days 2 and 3 i.e. for two days starting the day after daratumumab infusion to reduce the risk of delayed reactions

Additional Post-dose medications: the use of post-daratumumab medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. Following the first four doses, if the patient experiences no major IRRs, these inhaled post-daratumumab medications may be discontinued at the discretion of the physician.

CYCLE FREQUENCY

The cycle is repeated every 28 days until disease progression.

DOSE MODIFICATIONS

Renal and Hepatic Impairment

Renal	Hepatic
No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population PK analyses no dosage adjustment is necessary for patients with renal impairment	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

INVESTIGATIONS – during treatment

- FBC, U&Es, LFTs, Ca^{++}, glucose – every 3 - 4 weeks.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and for 3 months afterwards.
- Prophylactic fluconazole 50mg OD.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-3)), at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function

- Proton pump inhibitor or H2 antagonist at clinician's discretion on days of steroids
- Bone protection as per NSSG Bone Protection protocol MM.3

EMETIC RISK

Low risk

EXTRAVASATION RISK

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- **Interference with Serological Testing**
  Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test 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. The determination of a patient's ABO and Rh blood type are not impacted.

  I. Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.

  II. Patients must be typed and screened prior to starting daratumumab.

  III. Important information on safety and risk minimisation of Daratumumab and interference with Blood Compatibility Testing can be found of the summary of product characteristics on the following links:

  http://www.medicines.org.uk/emc/RMM.539.pdf
  http://www.medicines.org.uk/emc/RMM.545.pdf

  IV. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.

  V. Ask patients to tell their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.

- **Interference with Determination of Complete Response**
  Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma. On an adhoc basis DIRA assay (removes interference) can be organised through Janssen if required.
- **Contraception**
  To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.

- **Infusion reactions with subcutaneous injection:**

  Daratumumab solution for subcutaneous injection can cause severe and/or serious infusion-related reactions (IRRs), including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients.

The median time to onset of IRRs following injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia.

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. **If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. Daratumumab therapy should be discontinued immediately and permanently**.

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following daratumumab injection. Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

- **Risk of reactivation of hepatitis B virus (MHRA 2019):**

Hepatitis B virus reactivation has been reported in patients treated with daratumumab, including several fatal cases worldwide

All patients must be screened for hepatitis B virus before initiation of daratumumab; patients with unknown serology who are already on treatment should also be screened

Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment, and for at least 6 months following the end of daratumumab treatment

Patients with positive serology need to be advised to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation

Treatment with daratumumab should be stopped in patients with hepatitis B virus reactivation; appropriate treatment needs to be instituted in consultation with experts in the treatment of hepatitis B virus infection; consult with experts before resuming daratumumab in patients with adequately controlled viral reactivation

Suspected adverse drug reactions associated with daratumumab need to be reported to the Yellow Card Scheme

- **Other common adverse effects:**

  The most frequent adverse reactions of any grade (≥20 % patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

  With the exception of IRRs, the safety profile of the subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at ≥ 5% higher frequency for daratumumab subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

TREATMENT RELATED MORTALITY

<5%

REFERENCES

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DOCUMENT REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche	Co-trimoxazole to concomitant medication section. Re-wording of infusion rates	May 2016	1.1	May 2018
Manuela Sultanova Service Coordinator	Formatting	May 2016	1.2	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated hepatic impairment, concurrent medication and references	June 2017	1.3	June 2018
Network Protocol Review	Indication. Pre-assessment. Regimen pre- and post-medication. Renal hepatic impairment. Supportive medication. extravasation	June 2018	2.0	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Split dosing of first daratumumab dose	March 2019	2.1	June 2020
Protocol Review Day 2019	Pre-assessment, split dosing of first daratumumab dose, infusion rates and references	June 2019	2.2	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Addition of MHRA drug alert	October 2019	2.3	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Addition of SC daratumumab option during the COVID-19 pandemic	May 2020	2.5	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Timing of pre-meds updated	May 2020	2.6	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Significant update with standard SC daratumumab	June 2020	3.0	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	3.1	June 2021
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	3.2	June 2023

Appendix 1: intravenous daratumumab:

There may be a need to arrange for patient admission with the first infusion of intravenous daratumumab, where an extended duration of infusion is anticipated due to potential infusion-related reactions. Some day units are able to accommodate Cycle 1 Day 1, thus avoiding admission. Alternatively, to facilitate administration in the outpatient setting, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively.

From cycle 2 onwards, patients may qualify for rapid rate intravenous infusion. . See MM.48 (Daratumumab Rapid Rate Infusion) for further information.

DRUG REGIMEN
Cycles 1 &2

Pre-meds[b]	Paracetamol 1g PO, Montelukast 10mg PO on **(cycle 1 only)**, Chlorphenamine 10 mg IV Dexamethasone 20mg IV bolus or PO (give IV prior to the first infusion) (can be reduced to 12mg IV bolus or PO following the second infusion)	To be given 1 hour prior to daratumumab infusion
Daratumumab[a]	16mg/kg Intravenous infusion	Days 1, 8, 15 and 22
Post-infusion[c]	Dexamethasone 4mg PO	Days 2, 3, 9, 10, 16, 17 and 23, 24 i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions

[a]On the first week of cycle 1, there is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week.

[b]If daratumumab on the first week of therapy is administered as a split dose (8mg/kg days 1 and 2), the same pre-meds given on day 1 must also be given on day 2. Dexamethasone dose given as part of pre-meds on days 1 and 2 of the first week must be kept at 20mg

[c]If daratumumab on the first week of therapy is administered as a split dose (8mg/kg days 1 and 2), post-infusion dexamethasone must be given at 4mg on day 3 only

Cycles 3 to 6

Pre-meds	Paracetamol 1g PO, Chlorphenamine 10 mg IV Dexamethasone 12mg IV bolus or PO	To be given 1 hour prior to daratumumab infusion
Daratumumab	16mg/kg Intravenous infusion	Days 1 and 15
Post-infusion	Dexamethasone 4mg PO	Days 2,3 and 16,17

		i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions

Cycle 7- Onwards

Pre-meds	Paracetamol 1g PO, Chlorphenamine 10 mgIV Dexamethasone 12mg IV bolus or PO	To be given 1 hour prior to daratumumab infusion
Daratumumab	16mg/kg Intravenous infusion	Days 1
Post-infusion	Dexamethasone 4mg PO	Days 2 and 3 i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions

Additional Post-dose medications:

The use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

INFUSION RATES

Administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion.

	Dilution volume (Sodium chloride 0.9%)	**Initial rate (first hour)**	**Rate increment** [a]	**Maximum rate**
First week[a]	Option 1 (full dosing 16mg/kg) C1D1; 1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2 (split dosing 8mg/kg)			

	C1D1: 500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2 (split dosing 8mg/kg) C1D2: 500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second week[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Third and subsequent weeks[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions. **There is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week**

[b] A dilution volume of 500 mL should be used only if there were no ≥ Grade 1 IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

[c] A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no ≥ Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.

Notes:

1. For guidance on infusion rates **in the case of infusion related reactions**. See the managing infusion reactions section below.
2. From *cycle* 2 onwards, patients may qualify for rapid rate infusion. See MM.48 (Daratumumab Rapid Rate Infusion) for further information. Rapid Rate infusion is currently unlicensed.

Infusion-related reactions:

- Daratumumab can cause severe infusion-related reactions (IRR). Approximately half of all patients treated have experienced a reaction, the majority of IRRs occur at the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.
- Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include respiratory symptoms, such as 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-meds must be given 1 hour before the infusion. Patients must be monitored during the entire infusion.
- To reduce the risk of delayed infusion reactions, corticosteroids are given to all patients on the first and second day after all infusions
- 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**.**

- **Managing Infusion related reactions**
  For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. The infusion rate should be reduced when re-starting the infusion as outlined below. Management of infusion reactions may further require treatment discontinuation as outlined below.

IRR grade	Recommendation
Grade 1-2 (mild to moderate)	Once symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate up to the maximum rate of 200 mL/hour.
Grade 3 (severe)	Once symptoms resolve consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate. Permanently discontinue treatment upon the third occurrence of a Grade 3 or greater reaction.
Grade 4 (life threatening)	Permanently discontinue treatment.

Nursing Care Plan: Daratumumab Monotherapy

DARATUMUMAB: Monoclonal human antibody.
Indication: Relapsed/refractory Myeloma.
Frequency: 28 day cycles until disease progression.
Alopecia: No.
Emetic risk: Minimal.
Classification of extravasation: Neutral.

On cycle 1 day 1 send phenotyping bloods to the Transfusion Lab prior to Daratumumab infusion – send 3x EDTA tubes, all labelled with Safe Tx in a cross match sample bag, marked for the attention of a BMS 7. These bloods can be signed for on Aria once the sample has been sent. Please call the transfusion lab to let them know that phenotyping bloods are being sent because the patient is going to commence Daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of Daratumumab to red cells.

Administration: Sub cutaneous injection in the abdomen, approximately 7.5cm either side of the naval. Daratumumab is not approved to be given in any other injection sites.
IV infusion is available in a small minority of circumstances; SC administration is the standard of care.
Cycles 1-2 Daratumumab given on days 1, 8, 15 and 22.
Cycles 3-6 Daratumumab given on days 1 and 15.
Cycle 7 onwards Daratumumab given on day 1 only.
Side effects: Fatigue, bone marrow depression, thrombocytopenia, risk of infection, diarrhoea, constipation, anaemia.
Dosing reactions: Cough, fever, nasal irritation, wheezing, bronchospasm, hypotension, laryngeal and facial oedema, and urticaria/itching, anaphylaxis.
Reactions rarely occur after the first dose. **Patients are required to remain on the unit for 4 hours following Daratumumab injection on C1D1**. No observation period is necessary for subsequent injections.
Premeds are given 1-3 hours prior to Daratumumab, patients usually take these in advance from their TTO's after C1D1.

Regime Specific Considerations

- Ensure patients have been given a Patient ID Card for Daratumumab and are instructed to carry this for 6 months after stopping treatment; please check with Myeloma CNS team.
- Inject the SC dose of Daratumumab (15 mL) into the abdomen approximately 7.5 cm to the right or left of the navel over 5 minutes. Rotate injection sites for each dose. If the patient experiences pain or discomfort the injection can be paused. If necessary the remainder of the injection can be given on the other side of the abdomen.
- Bloods (including glucose) are required at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.
- Advise patients to maintain fluid intake of 2-3 litres a day and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- **IV Daratumumab only** - administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Rapid rate can be given from cycle 2 as long as there has been no reaction to the previous dose and this was given in 500mls rather than 1 litre of fluid. Montelukast needs to be given before the first rapid rate infusion.
- Montelukast is given as a premed pre SC/IV Daratumumab on C1 only.