Chemotherapy Protocol

Myeloma

DVd-T SC Bortezomib-Daratumumab-Dexamethasone-Thalidomide

Regimen

- Myeloma – DVd-T SC Bortezomib-Daratumumab-Dexamethasone-Thalidomide

Indication

- Daratumumab in combination with bortezomib, dexamethasone and thalidomide is recommended for use within the Cancer Drugs Fund as an option for treating newly diagnosed multiple myeloma patients who are eligible for transplant.

- This regimen was based on CASSIOPEIA trial and has been slightly modified to simplify the schedule (e.g. SC instead of IV daratumumab and, weekly bortezomib instead of twice-weekly, and dexamethasone days 22-23 on cycles 3-6). Ensure the correct regimen and cycle is selected.

- NICE approval stipulates that cycles 1-4 will be given prior to autologous stem cell transplant then cycle 5-6 will be given post autologous stem cell transplant.

Toxicity

Drug	Adverse Effect
Bortezomib	GI disturbances, peripheral neuropathy, hypotension, dizziness, blurred vision, headache, musculoskeletal pain, pyrexia
Daratumumab	Infusion related reactions, hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, respiratory tract infections (including pneumonia), neutropenia, thrombocytopenia, anaemia, lymphopenia, peripheral neuropathy, diarrhoea, muscle spasms, fatigue, pyrexia and peripheral oedema, blood transfusion related events
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, Cushingoid changes, glucose intolerance.
Thalidomide	Drowsiness, constipation, dizziness, increased risk of thromboembolic events, dry skin/rash, peripheral neuropathy, teratogenicity, syncope, bradycardia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Bloods

- FBC, U&Es, Ca^{2+} and LFTs prior to day one of each cycle of treatment.

- Paraprotein and / or light chains prior to each cycle.

- All patients should be tested for hepatitis B virus (HBV) before initiating treatment with daratumumab. Those patients who test positive for HBV infection should be discussed with a consultant specialising in HBV prior to initiating treatment with daratumumab to plan monitoring requirements whilst on treatment. Patients may also be tested for hepatitis C, CMV and HIV at the same time if clinically appropriate.

- Send a blood 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.

- Regular monitoring of blood glucose is considered good practice due to dexamethasone use.

- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained within 3 days of starting thalidomide the test must be repeated every 4 weeks (every 2 weeks in women with irregular menstrual cycles) with the final test 4 weeks after the last dose of thalidomide

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. Always refer to the responsible consultant, as any dose delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L).

Consider growth factor support as an alternative to the options below, particularly where there is evidence of bone marrow suppression.

To initiate a new cycle of daratumumab, the neutrophil count should be $1x10^9$/L or greater and the platelet count should be $50x10^9$/L or greater, unless the low counts are due to bone marrow infiltration with myeloma. In this situation the daratumumab may be administered at the discretion of the treating consultant haematologist with the appropriate blood product and growth factor support.

Neutrophils ($x10^9$/L)	Dose Modifications (Daratumumab and Bortezomib)
Less than $0.5x10^9$/L or febrile neutropenia (fever greater	Interrupt daratumumab treatment and monitor FBC weekly. Once neutrophils recover to $1x10^9$/L, resume daratumumab

than or equal to 38.5°C and neutrophils less than 1)	Bortezomib - Consider treatment delay or dose reduction or growth factor support. Seek consultant advice.
Platelets (x10^9/L)	**Dose Modifications**
Daratumumab Less than 50x10^9/L	Interrupt daratumumab treatment and monitor FBC weekly. Once platelets recover to 50x10^9/L or greater resume daratumumab
Bortezomib Less than 25x10^9/L	Consider treatment delay or dose reduction or platelet transfusion. Seek consultant advice.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	**Bilirubin µmol/L**		**AST/ALT units/L**	**Dose (% of original dose)**
Bortezomib	1.5xULN or below		N/A	100%
	greater than 1.5xULN		N/A	Initiate treatment at 0.7mg/m^2. The dose may be escalated to 1mg/m^2 or reduced to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
Thalidomide	N/A		N/A	No dose modification required
Daratumumab	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population pharmacokinetic analysis no dosage adjustments are necessary for patients with hepatic impairment			

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Bortezomib	greater than 20	100%
	20 and below	Clinical decision
Thalidomide	N/A	No dose modification required
Daratumumab	No adjustments necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes

Bortezomib

For patients experiencing NCI-CTC grade 1 neuropathy without loss of function or pain continue with full dose bortezomib.

For NCI-CTC grade 1 with pain or grade 2 neuropathy reduce the dose of bortezomib to 1mg/m^2.

For NCI-CTC grade 2 with pain or grade 3 neuropathy discontinue treatment until symptoms have resolved to NCI-CTC grade 1 or less then reinitiate bortezomib at a dose of 0.7mg/m^2 For NCI-CTC grade 4 neuropathy and/or severe autonomic neuropathy discontinue bortezomib.

For any other NCI-CTC grade 3 non haematological toxicity bortezomib should be discontinued until symptoms have resolve to NCI-CTC grade 1 or below. On the first occurrence treatment may be reinitiated at a dose of 1mg/m^2. Following second occurrence to dose should be further reduced to 0.7mg/m^2 once symptoms have resolved.

If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Thalidomide

Peripheral Neuropathy

If NCI-CTC grade 1 neurological toxicity occurs treatment may be continued, if symptoms worsen consider dose reduction or interruption. Treatment may be reintroduced at a reduced dose if symptoms resolve. If NCI-CTC grade 2 neurological toxicity occurs suspend treatment or reduce the dose by at least 50%. Treatment may be reintroduced at a reduced dose if symptoms resolve to grade 1 or below. For NCI-CTC neurological toxicity grade 3 or above or toxicity that does not resolve despite treatment interruption / dose reduction thalidomide treatment should be stopped.

Thromboembolism

The thrombotic risk for patients commencing on thalidomide must be assessed. Appropriate thromboprophylaxis must be prescribed according to local policies. Thromboprophylaxis is generally recommended for at least the first 5 months of thalidomide treatment, especially in patients with additional thrombotic risk factors. Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain or swelling of a limb.

The occurrence of a thromboembolic event such as a DVT or thromboembolism, notably pulmonary embolism, is an indication for full anticoagulation following standard treatment guidelines. Thalidomide may be stopped, but can be re-introduced, initially at 50mg daily with escalation at subsequent cycles to 100mg, assuming good anticoagulant control and no other untoward side effects.

All patients should be initially prescribed a low molecular weight heparin at the appropriate prophylactic dose. Therapeutic warfarin is an alternative to low molecular heparin. Aspirin 75mg each morning is an alternative in very low risk patients once a response has been obtained.

Teratogenicity

Thalidomide is highly teratogenic.

All prescribers, patients and pharmacy staff must comply with the manufacturer's Pregnancy Prevention Programme.

Women of child-bearing potential taking thalidomide must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. They must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping thalidomide (or every 2 weeks in women with irregular menstrual cycles). If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately and seek medical advice.

Men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

Other

For other thalidomide related toxicities of NCI-CTC grade 3 or above. Stop thalidomide until recovery to NCI-CTC grade 1 or below. Cautious reintroduction of thalidomide at a dose of 50mg a day may be considered with dose escalation if tolerated.

Dexamethasone

For patients who are elderly or unable to tolerate the standard dose of dexamethasone the dose given the day after bortezomib alone may be reduced. Please note the doses before and the day after each daratumumab are to reduce the risk of infusion related reactions and as a steroid component of the triple combination.

Infusion related reactions (IRR)

Daratumumab solution for subcutaneous injection can cause severe and/or serious 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 daratumumab 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, pruritus, 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.

Interference with Serological Testing

Daratumumab binds to CD38 in red blood cells and results in a positive indirect antiglobulin test (Coombs test). Daratumumab mediated positive indirect antiglobulin test may persist for up to six months after the last daratumumab infusion. Daratumumab bound red blood cells masks detection of antibodies to minor antigens in the patients serum. The determination of a patients ABO and Rh blood type are not impacted.

Blood transfusion must be informed that a patient is receiving daratumumab. Patients must be typed and screened prior to daratumumab. All patients must be given an identification card that should be carried for six months after stopping therapy and agree to inform all healthcare professionals who treat them that they have received daratumumab.

Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum electrophoresis and immunofixation 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.

Reactivation of Hepatitis B Virus

Hepatitis B virus reactivation has been reported in patients treated with daratumumab. All patients must be screened for hepatitis B before initiation of treatment. This includes all patients with unknown serology who are on treatment already.

Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment and for at least six months after completion of daratumumab. Those with positive serology must seek medical help immediately if they experience symptoms of hepatitis B. Daratumumab must be stopped if hepatitis B reactivation occurs during treatment.

Regimen

28 day cycle

Cycles 1 to 2

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1,8,15,22	Subcutaneous
Daratumumab	1800mg	1,8,15,22	Subcutaneous
Dexamethasone	20mg	1,2, 8,9,15,16,22,23	20mg Oral Reduce dose to 10mg orally (or iv dose equivalent) in over 75yrs
Thalidomide	50-100mg PO Start at 50mg and increase as tolerated	Daily	Oral

Cycles 3 to 6

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1,8,15,22	Subcutaneous
Daratumumab	1800mg	1,15	Subcutaneous
Dexamethasone	20mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, the pre-med dose of dexamethasone is sufficient. On non-daratumumab days, 20mg is to be administered.	1,2, 8,9,15,16,22,23	20mg Oral Reduce dose to 10mg orally (or iv dose equivalent) in over 75yrs
Thalidomide	50-100mg PO Start at 50mg and increase as tolerated	Daily	Oral

NICE approval stipulates that cycles 1-4 will be given prior to autologous stem cell transplant then cycle 5-6 will be given post autologous stem cell transplant.

Dose Information

- Bortezomib dose will be dose banded in accordance with the national dose bands (2.5).
- Dexamethasone is available as 2mg and 500microgram tablets and 3.3mg in 1ml injection (equivalent to 4mg orally)
- Thalidomide is available as 50mg capsules

Administration Information

- If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.
- Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.
- For first dose a cannula should be inserted to allow emergency treatment of anaphylaxis

- First dose daratumumab that the patient should be observed with hourly observations for 4 hours following subcutaneous administration. If no infusion-related reactions following the first dose then neither cannulation nor additional post injection observations are needed with subsequent doses. If IRR with first dose then continue to observe for 4 hours following subsequent doses until IRRs subside.

- 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 umbilicus 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 medicinal products for subcutaneous use at the same site as Daratumumab.

- Thalidomide should be taken at night to avoid daytime drowsiness

- Thalidomide prescriptions must be accompanied by a completed Prescription Authorisation Form

Additional therapy

- Consider allopurinol 300mg once a day for seven days for the first cycle only oral

- Anti-emetics

  - metoclopramide 10mg three times a day when required oral (this is not included in the regimen on ARIA but can be added from favourites if required)

- Premedication required 1 to 3 hours before every daratumumab infusion:

  - dexamethasone – see regimen for dose details
  - chlorphenamine 4mg oral
  - paracetamol 1000mg oral
  - montelukast 10mg oral for the first four doses only

- Thromboprophylaxis according to local formulary choice. For example;
  - dalteparin 5000units once a day subcutaneous injection
  - enoxaparin 40mg once a day subcutaneous injection
  - heparin 5000units twice a day subcutaneous injection

- Consider anti-infective prophylaxis including:

  - aciclovir 400mg twice a day oral

- co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
- fluconazole 100mg once a day oral if recurrent oral candidiasis

- Bisphosphonates in accordance with local policies.

- Mouthwashes according to local or national policy on the treatment of mucositis.

- Laxatives as required for thalidomide-induced constipation

- Gastric protection with a proton pump inhibitor or an H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

- As required for the treatment of infusion related reactions for patients at high risk of respiratory complications:

  - salbutamol 2.5mg nebulised
  - hydrocortisone sodium succinate 100mg intravenous
  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral
  - oxygen as required

Additional Information

- All instances of infusion related reaction must be recorded on ARIA.

- Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered.

- Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.

- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.

- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

- For all patients taking thalidomide; the patient, prescriber and supplying pharmacy must comply with an appropriate pregnancy prevention programme.

Ref
1. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics, Janssen, February 2019
2. Darzalex ® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen, Jan 2019
3. Thalidomide, Celgene® eMC UK Summary of Product Characteristics, Celgene, April 2019
4. Maria-Victoria Mateos , Hareth Nahi , Wojciech Legiec , Sebastian Grosicki , Vladimir Vorobyev , Ivan Spicka , Vania Hungria , Sibirina Korenkova , Nizar Bahlis , Max Flogegard , Joan Bladé , Philippe Moreau , Martin Kaiser , Shinsuke Iida , Jacob Laubach, Hila Magen, Michele Cavo, Cyrille Hulin, Darrell White, Valerio De Stefano, Pamela L Clemens, Tara Masterson, Kristen Lantz, Lisa O'Rourke , Christoph Heuck , Xiang Qi , Dolly A Parasrampuria , Zhilong Yuan , Steven Xu, Ming Qi , Saad Z Usmani. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematology. Volume 7, ISSUE 5, e370-e380, May 01, 2020
5. Philippe Moreau et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38.

REGIMEN SUMMARY

Myeloma – DVd T SC Bortezomib-Daratumumab-Dexamethasone-Thalidomide

Cycle 1 Day 1

1. Warning – Inform blood transfusion
   Administration Instructions
   Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered.

   Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response

   Please inform blood transfusion when a patient is prescribed daratumumab

2. Antihistamine oral
   Administration Instructions
   Oral antihistamine according to local formulary choices. To be taken 1 -3 hours prior to daratumumab infusion
   For example;
   Chlorphenamine 4mg Oral
   Loratadine 10mg Oral
   Cetirizine 10mg Oral
   Fexofenadine 120mg Oral
   Acrivastine 8mg Oral

3. Dexamethasone 20mg oral
   Administration Instructions
   Can be administered as 20mg intravenous. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

4. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

5. Montelukast 10mg oral
   Administration Instructions
   Take 1-3 hours prior to daratumumab

6. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
   Administration Instructions
   Inject the 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 medicinal products for subcutaneous use at the same site as daratumumab.

7. Bortezomib 1.3mg/m^2 subcutaneous injection

8. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

9. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

10. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

11. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycle 1 Days 8, 15, 22

12. Warning – Check if Antihistamine Taken
    Administration Instructions
    Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice; To be taken 1 -3 hours prior to daratumumab infusion
    Chlorphenamine 4mg Oral
    Loratadine 10mg Oral
    Cetirizine 10mg Oral
    Fexofenadine 120mg Oral
    Acrivastine 8mg Oral

13. Warning – Check if the Dexamethasone Taken
    Administration Instructions
    Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

14. Warning – Check if the Paracetamol Taken
    Administration Instructions
    Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

15. Montelukast 10mg oral

16. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
    Administration Instructions
    Inject the 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 medicinal products for subcutaneous use at the same site as daratumumab.

17. Bortezomib 1.3mg/m^2 subcutaneous injection

18. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

19. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

20. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

21. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycle 1 Take home medicines (day 1 only)

22. Warning – Pregnancy Prevention Programme
    Administration Instructions
    Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

23. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

24. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning prior to daratumumab injection
    Note to pharmacy; dispense for day 1 of the next cycle

25. Thalidomide 50mg once a day for 28 days oral
    Administration Instructions
    Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.
    Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
    Take at night to avoid daytime drowsiness. To start at 50mg and escalate to 100mg if appropriate

26. Allopurinol 300mg once a day for 7 days oral
    Administration information
    Take in the morning with food and plenty of water. This should be supplied for the first cycle only.

27. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

28. Levofloxacin 500mg once a day for 84 days oral
    Administration Instructions
    Please supply 12 weeks on cycle 1 only

29. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

30. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;

    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    - ranitidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

31. Anthistamine on the days of daratumumab administration
    Administration Instructions
    Take on the day of daratumumab administration. To be taken 1 -3 hours prior to daratumumab infusion Please supply 1 x OP. This is to cover all cycles. To be supplied as per local formulary choice

Chlorphenamine 4mg Oral
Loratadine 10mg Oral
Cetirizine 10mg Oral
Fexofenadine 120mg Oral
Acrivastine 8mg Oral

32. Paracetamol 1000mg oral on the days of daratumumab administration
    Administration Instructions
    Take 1000mg prior to daratumumab administration. To be taken 1 -3 hours prior to daratumumab infusion Please supply 1 x 100 x 500mg. This is to cover all cycles

33. Thromboprophylaxis according to local formulary choice;
    Administration Instructions
    The choice of thromboprophylaxis is dependent on local formulary choice and may include;
    - dalteparin 5000units once a day subcutaneous injection
    - enoxaparin 40mg once a day subcutaneous injection
    - heparin 5000units twice a day subcutaneous injection

    Please supply 28 days or nearest original pack size.

Cycles 2 days 1, 8, 15, 22

34. Warning – Check if Antihistamine Taken
    Administration Instructions
    Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
    - Chlorphenamine 4mg Oral
    - Loratadine 10mg Oral
    - Cetirizine 10mg Oral
    - Fexofenadine 120mg Oral
    - Acrivastine 8mg Oral

35. Warning – Check if the Dexamethasone Taken
    Administration Instructions
    Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

36. Warning – Check if the Paracetamol Taken
    Administration Instructions
    Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

37. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
    Administration Instructions
    Inject the 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 medicinal products for subcutaneous use at the same site as daratumumab.

38. Bortezomib 1.3mg/m^2 subcutaneous injection

39. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

40. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

41. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

42. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycles 2 Take home medicines (day 1 only)

43. Warning – Pregnancy Prevention Programme
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

44. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

45. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning prior to daratumumab injection. Reduce dose to 10mg in patients over 75 years old.
    Note to pharmacy; dispense for day 1 of the next cycle

46. Thalidomide 50mg once a day for 28 days oral
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg. Take at night to avoid daytime drowsiness. To start at 50mg and escalate to 100mg if appropriate

47. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

48. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

49. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;

    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    - ranitidine 150mg twice a day oral

    Please supply 28 days or the nearest original pack size.

50. Thromboprophylaxis according to local formulary choice;
    Administration Instructions
    The choice of thromboprophylaxis is dependent on local formulary choice and may include;
    - dalteparin 5000units once a day subcutaneous injection
    - enoxaparin 40mg once a day subcutaneous injection
    - heparin 5000units twice a day subcutaneous injection

    Please supply 28 days or nearest original pack size.

Cycles 3 to 6 day 1 and 15

51. Warning – Check if Antihistamine Taken
    Administration Instructions
    Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
    Chlorphenamine 4mg Oral
    Loratadine 10mg Oral
    Cetirizine 10mg Oral
    Fexofenadine 120mg Oral
    Acrivastine 8mg Oral

52. Warning – Check if the Dexamethasone Taken
    Administration Instructions
    Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose. Reduce dose to 10mg intravenous equivalent or 10mg orally in patients over 75 years old.

53. Warning – Check if the Paracetamol Taken
    Administration Instructions
    Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

54. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
    Administration Instructions
    Inject the 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 medicinal products for subcutaneous use at the same site as daratumumab.

55. Bortezomib 1.3mg/m^2 subcutaneous injection

56. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

57. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

58. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

59. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

Cycles 3 to 6 days 8 and 22

60. Bortezomib 1.3mg/m^2 subcutaneous injection

Cycles 3,4,5 Take home medicines (day 1 only)

61. Warning – Pregnancy Prevention Programme
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

62. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

63. Dexamethasone 20mg on day 1 of the next cycle
    Administration Information
    Take in the morning of daratumumab injection. Reduce dose to 10mg in patients over 75 years old.
    Note to pharmacy Note to pharmacy; dispense for day 1 of the next cycle

64. Thalidomide 50mg once a day for 28 days oral
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg. Take at night to avoid daytime drowsiness. To start at 50mg and escalate to 100mg if appropriate

65. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

66. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

67. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;
        - esomeprazole 20mg once a day oral
        - omeprazole 20mg once a day oral
        - lansoprazole 15mg once a day oral
        - pantoprazole 20mg once a day oral
        - rabeprazole 20mg once a day oral
        - cimetidine 400mg twice a day oral
        - famotidine 20mg once a day oral
        - nizatidine 150mg twice a day oral
        - ranitidine 150mg twice a day oral
    Please supply 28 days or the nearest original pack size.

68. Thromboprophylaxis according to local formulary choice;
    Administration Instructions
    The choice of thromboprophylaxis is dependent on local formulary choice and may include;
        - dalteparin 5000units once a day subcutaneous injection
        - enoxaparin 40mg once a day subcutaneous injection
        - heparin 5000units twice a day subcutaneous injection
    Please supply 28 days or nearest original pack size.

Cycle 6 Take home medicines (day 1 only)

69. Warning – Pregnancy Prevention Programme
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients

70. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

71. Thalidomide 50mg once a day for 28 days oral
    Administration Instructions Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg. Take at night to avoid daytime drowsiness. To start at 50mg and escalate to 100mg if appropriate

72. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions
Please supply 28 days or an original pack if appropriate.

73. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

74. Gastric Protection

Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please supply 28 days or the nearest original pack size.

75. Thromboprophylaxis according to local formulary choice;

Administration Instructions
The choice of thromboprophylaxis is dependent on local formulary choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	Mar 2022	None	Nanda Basker Pharmacist	Dr Mathew Jenner Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.