SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

DRd
DARATUMUMAB, LENALIDOMIDE & DEXAMETHASONE
Multiple Myeloma

PROTOCOL REF: MPHADLDMM
(Version No. 1.0)

Approved for use in:

- Patients with previously untreated multiple
- myeloma ***(1st line treatment)*** who are ineligible for stem cell transplant.

Blueteq registration required prior to initiation

Dosage:

Drug	Dose	Route	Frequency
Cycle 1 & 2			
Daratumumab	**1800mg**	SC	Days 1, 8, 15 & 22
Lenalidomide	**25mg once daily**	PO	Day 1 to 21
Dexamethasone	**40mg once WEEKLY***	PO	Days 1, 8, 15 and 22
Cycle 3 to 6			
Daratumumab	**1800mg**	SC	Days 1 & 15
Lenalidomide	**25mg once daily**	PO	Day 1 to 21
Dexamethasone	**40mg once WEEKLY***	PO	Days 1, 8, 15 and 22
Cycle 7 onwards			
Daratumumab	**1800mg**	SC	Day 1
Lenalidomide	**25mg once daily**	PO	Day 1 to 21
Dexamethasone	**40mg once WEEKLY***	PO	Days 1, 8, 15 and 22

*Reduce dexamethasone to 20mg if >75 years old or at clinician discretion.

Cycle length: every 28 days. Continue until disease progressions or intolerance.

Administration:

- Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
- If a lenalidomide dose is missed and <12hours late the missed dose should be taken. Missed doses >12hours should be omitted and the next dose taken as scheduled.
- Dexamethasone tablets should be taken in the morning after food.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme and provide patients with appropriate patient educational brochure and patient card.
- **Due to the risk of injection-related reactions (IRRs), pre-medications should be administered approximately 1 to 3 hours before each daratumumab injection.**
- Dexamethasone is being used as both chemotherapy agent and also to prevent delayed daratumumab IRRs - counsel patients on the importance of these. In the absence of IRRs post-infusion dexamethasone can be stopped following the 3rd dose of daratumumab.
- Daratumumab interferes with indirect antiglobulin test (**indirect Coombs test**). Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test, which may persist for up to 6 months after the last daratumumab administration. Patients should be typed and screened prior to starting daratumumab. Phenotyping should be undertaken prior to commencing treatment as per local practice. In the event of a planned transfusion, blood transfusion centres should be notified of this interference with indirect antiglobulin tests. See SPC for further details.

Pregnancy Prevention Programme:

Due to the increased risk of birth defects associated fetal exposure to lenalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation with lenalidomide

- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of lenalidomide. This must be approved by a pharmacist when verifying each prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.
- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

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 immediately.
- 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:

Low risk

Supportive treatments:

Daratumumab Pre - injection Medications

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

- Montelukast 10mg oral STAT (prior to cycle 1 only but continue if COPD/Asthma)
- Paracetamol 1000mg oral STAT
- Chlorphenamine 4mg oral STAT
- Dexamethasone 40mg oral prior to daratumumab

Supportive Medications

- Allopurinol 300mg daily for 28 days (cycle one only)
- Aciclovir 400mg twice daily
- Co-trimoxazole 480mg once daily
- Dexamethasone 4mg once daily for 2 days after each dose of daratumumab. This can be stopped if no IRR's after 3rd dose of daratumumab.
- Nystatin 1mL four times daily **OR** Fluconazole 50mg once daily for antifungal prophylaxis (if higher doses of steroids being used - review each cycle)
- Omeprazole 20mg once daily - review each cycle
- Ondansetron 8mg twice daily when required, usually prescribed for cycle 1 only
- VTE prophylaxis:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic LMWH)
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
    - Aspirin 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine Clearance (mL/min)	**Dose Adjustment**
Lenalidomide	30 – 50	10mg once daily*
	<30 not requiring dialysis	15mg alternate days
	End stage renal disease (<30)	5mg once daily. If on dialysis, administer after dialysis.
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.	

*The dose may be escalated to 15mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment

Hepatic Dose Modifications	
Lenalidomide	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.
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:

Daratumumab – No known drug interactions

Lenalidomide:

- Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.
- **Digoxin** – concomitant administration with lenalidomide increased plasma exposure of digoxin, monitoring of the digoxin concentration is advised during lenalidomide treatment.
- **Statins** – there is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

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

Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
Cycle 1 & 2				
1, 8, 15 & 22	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone*	**40mg**	**Oral**	
	Montelukast**	**10mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
2, 3, 9, 10, 16, 17, 23, 24	**Dexamethasone**	**4mg**	**Oral**	TTO: Once daily for 2 days after each dose of daratumumab (can stop after 3rd dose in absence of IRRs)
1 to 21	**Lenalidomide**	**25mg**	**Oral**	TTO: Once daily
Cycle 3 to 6				
1 & 15	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone*	**40mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
1	**Dexamethasone***	**40mg**	**Oral**	TTO: Day 1, 8, 15 and 22 (give prior to daratumumab on days 1 & 8 as above)
1 to 21	**Lenalidomide**	**25mg**	**Oral**	TTO: Once daily
Cycle 7 onwards				
1	**Paracetamol**	**1g**	**Oral**	60 minutes prior to daratumumab
	Chlorphenamine	**4mg**	**Oral**	
	Dexamethasone*	**40mg**	**Oral**	
	Daratumumab	**1800mg**	**SC**	Over 3-5 minutes
	Dexamethasone*	**40mg**	**Oral**	TTO: Days 1, 8, 15 & 22 (give prior to daratumumab on day 1 as above)
1 to 21	**Lenalidomide**	**25mg**	**Oral**	TTO: Once daily

*Reduce dexamethasone at clinician discretion

** Prior to cycle 1 only but continue if COPD/Asthma

Main toxicities:

Lenalidomide
Neutropenia, thrombocytopenia, anaemia, infections, peripheral neuropathy, MDS, hypokalaemia, VTE, constipation, diarrhea, nausea, vomiting, rash, dry skin, muscle spasm, fatigue
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	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment + PS recorded	X	X	X	X	Prior to every cycle
SACT Assessment	X	X	X	X	Prior to every cycle
FBC	X	X	X	X	(Weekly for the first month and then monthly thereafter unless clinically indicated). Prior to every cycle
Celgene Pregnancy Prevention Program Consent	X				
Celgene prescription authorization form		X	X	X	Prior to each supply
U&E & LFTs, CrCl (Cockcroft and Gault)	X	X	X	X	Prior to every cycle
Bone profile	X				As clinically indicated
Virology screen Hep B and C/HIV	X				
Dental assessment	X				As clinically indicated
HbA1C	X				As clinically indicated
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X	X	X	Prior to every cycle
Neurological assessment (for neuropathy)	X	X	X	X	Prior to every cycle
Blood Pressure, pulse, temperature and respiratory rate		X	X	X	On days of daratumumab
Blood glucose	X				Repeat if clinically indicated
Imaging as per NICE/network guidance and clinical indication	X				To restage as indicated
Pregnancy test	X	X	X	X	Each cycle if clinically indicated
Thyroid function test	X				If clinically indicated
Height	X				
Weight	X	X	X	X	Prior to every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle should proceed if:

ANC is ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L

Dose step reductions:

Dose Level	Lenalidomide	Dexamethasone
Starting dose	25mg	40mg
Dose level 1	20mg	20mg
Dose level 2	15mg	12mg
Dose level 3	10mg	8mg
Dose level 4	5mg	4mg
Dose level 5	2.5mg	Not applicable

Dose reduction for both products can be managed independently

Thrombocytopenia:

When platelets	Recommended course
Fall to < 30 x 10^9/L	Stop lenalidomide dosing for remainder of cycle*
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

*If dose limiting toxicity occurs on > day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28 day cycle.

Neutropenia:

If neutropenia is the only toxicity at any dose level, consider adding G-CSF and maintain the dose level of lenalidomide.

When neutrophils	Recommended course
First fall to <1.0 x 10^9/L	Interrupt lenalidomide treatment
	If neutropenia is the only observed toxicity: Resume lenalidomide at starting dose once daily when returns to ≥ 1.0 x 10^9/L

	If dose-dependent haematological toxicities other than neutropenia are observed: Reduce dose by one dose level – resume once daily when returns to ≥ 1.0 x 10^9/L
For each subsequent drop below < 1.0 x 10^9/L	Interrupt lenalidomide treatment
	Resume lenalidomide at next lower dose level once daily when returns to ≥ 1.0 x 10^9/L

For haematological toxicity the dose of lenalidomide may be re-introduced to the next higher dose level upon improvement in bone marrow function (no haematological toxicity for at least 2 consecutive cycles, ANC ≥ 1.5 x 10^9/L, with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

Non- Haematological toxicity:

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation from these reactions.

Daratumumab Injection-related reactions:

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

First Injection
Monitor patient for 4 hours post infusion including blood pressure, pulse, temperature and respiratory rate pre-injection and every 30 minutes thereafter
Second and subsequent Injection
There is no need to routinely monitor blood pressure, pulse, temperature and respiratory rate. Keep patients for 30 minutes after injection, can be sent home if feel well. **Note patients should be kept for longer if they experienced a grade 2+ IRR during their previous injection.** Severe reactions can occur, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms noted predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension. Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab. Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose. Medical management/supportive treatment for IRRs should be instituted as needed. Daratumumab therapy should be permanently discontinued in the event of life-threatening IRRs.

References:

1. Summary of Product Characteristics Daratumumab. Janssen-Cilag Ltd. Last updated 24th May 2023 [accessed on Oct 2023]
2. Summary of Product Characteristics. Lenalidomide. Zentiva. Last updated July 2023 [accessed on Oct 2023]
3. NICE TA917 – Daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when stem cell transplant is unsuitable. Published: 25th Oct 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

Date added into Q-Pulse	1st February 2024
Date document posted on the Intranet	

Version History

Date	Version	Author name and designation	Summary of main changes
Nov 2023	1.0	**Jennifer Gibson (Principal Pharmacist Haematology)**	**New protocol**