Daratumumab (SC 1800mg), Bortezomib and dexAMETHasone Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Daratumumab in combination with bortezomib and dexAMETHasone in adult patients with multiple myeloma who have received at least one prior therapy	C90	00609a	ODMS 01/10/2020

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The dosing schedule for daratumumab (which is administered as a subcutaneous injection) in combination with bortezomib and dexAMETHasone is based on a 21 day cycle regimen as detailed in the treatment table below (Table 1) for a total of 24 weeks followed by daratumumab monotherapy every 28 days until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered

Table 1: Treatment table for daratumumab, bortezomib and dexAMETHasone

Cycle 1-3 (week 1-9, total of 9 doses of daratumumab)

Day	Drug	Dose	Route	Diluent and Rate	Cycle frequency
1,8,15	Daratumumab[a]	1800mg	S.C	Over 3 to 5 minutes	21 days
1,4,8,11	Bortezomib[b,c]	1.3mg/m^2	S.C	n/a	21 days
1, 2, 4, 5, 8, 9, 11 and 12,	dexAMETHasone[d, e]	20mg	PO	n/a	21 days

Cycle 4 -8 (week 10-24, total of 5 doses of daratumumab)

Day	Drug	Dose	Route	Diluent and Rate	Cycle frequency
1	Daratumumab[a]	1800mg	S.C	Over 3 to 5 minutes	21 days
1,4,8,11	Bortezomib[b,c]	1.3mg/m^2	S.C	n/a	21 days
1, 2, 4, 5, 8, 9, 11 and 12	dexAMETHasone[d, e]	20mg	PO	n/a	21 days

Cycle 9 onwards (week 25 onwards)

Day	Drug	Dose	Route	Diluent and Rate	Cycle frequency
1	Daratumumab[a]	1800mg	S.C	Over 3 to 5 minutes	28 days

[a] If a planned dose of daratumumab is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

[b] Consideration may be given to use of bortezomib 1.3mg/m^2 once weekly in patients who experienced neuropathy previously or those with pre-existing neuropathy.

[c] The solution should be injected subcutaneously, at a 45-90^0 angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered SC or a switch to IV injection is recommended.
At least 72 hours should elapse between consecutive doses of bortezomib.
Bortezomib is a proteasome inhibitor and is neurotoxic. **Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer**. *Here*

[d] Additional background corticosteroids should not be given on daratumumab dosing days when the patient has received dexAMETHasone as a pre-medication.
On the days of daratumumab administration the scheduled dose of dexAMETHasone is administered as a premedication prior to dosing rather than taken by the patient at home.

[e] A reduced dose of 20 mg/week may be considered for patients >75 years, for patients with a Body Mass Index (weight in kg divided by the square of the height in metres) <18.5 and for patients with poorly controlled diabetes mellitus or prior intolerance/adverse event to steroid therapy.
Consideration should be given to the recommendation for the administration of an oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local policy) the day after the daratumumab dose for the prevention of delayed infusion related reactions (IRRs).

Table 2: Dosing schedule for cycle 1-3

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Daratumumab	✓							✓							✓						
Bortezomib	✓			✓				✓			✓										
dexAMETHasone	✓	✓		✓	✓			✓	✓		✓	✓									

Table 3: Dosing schedule for cycle 4-8

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Daratumumab	✓																				
Bortezomib	✓			✓				✓			✓										
dexAMETHasone	✓	✓		✓	✓			✓	✓		✓	✓									

ELIGIBILITY:

- Indication as above
- ECOG 0-2
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy.

EXCLUSIONS:

- Hypersensitivity to daratumumab, bortezomib or any of the excipients
- Refractory to bortezomib or other proteasome inhibitor
- Pregnancy, breast feeding
- Severe uncontrolled asthma/obstructive airways disease

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Uric acid
- Urine pregnancy testing for pre-menopausal women < 55 years
- 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.
- Virology screen - EBV, CMV, Hepatitis B (HBsAg, HBcoreAb) & C, HIV ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**
- Blood pressure, Blood glucose* if being treated with oral hypoglycaemics (*See Drug Interactions)
- Assessment of peripheral neuropathy status

Regular tests:

- FBC; monitor platelet count **at a minimum** of day 1 and day 11 each cycle.
- Renal, liver and bone profile
- Blood pressure, Blood glucose* if being treated with oral hypoglycaemics (*See Drug Interactions)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- 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- See table 5 below
- Bortezomib therapy should be withheld when the platelet count is < 25 x 10^9/L
- Consider supportive care with transfusions or growth factors.

Table 4: Dose reduction steps for bortezomib

Dose Level	Dose
Starting dose	1.3mg/m^2
Dose level 1	1.0mg/m^2
Dose level 2	0.7mg/m^2
Dose level 3	Discontinue

Haematological:

Table 5: Dose modification of daratumumab and bortezomib for haematological toxicity

Drug	ANC (x10^9/L)		Platelets (x10^9/L)		Dose Modification
Daratumumab	≥0.5-1	Or	≥25-50	With bleeding	Consider withholding treatment until symptoms of the toxicity have resolved
	<0.5	Or	<25		Consider withholding treatment until symptoms of the toxicity have resolved
Bortezomib	<0.5	Or	<25		Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at the next lower dose level 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

Renal and Hepatic Impairment:

Table 6: Recommended dose modification for renal or hepatic impairment

Drug	Renal impairment	Hepatic impairment			
Daratumumab	No formal studies of daratumumab in patients with renal impairment have been conducted. Based on a population pharmacokinetic (PK) analysis 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			
Bortezomib	No dose adjustment is needed Haemodialysis: No dose adjustment is needed	**Grade of Hepatic Impairment***	**Bilirubin Level**	**(AST) levels**	**Modification of starting dose**
		Mild	≤1 x ULN	> ULN	None
			>1-1.5xULN	Any	None
		Moderate	>1.5-3xULN	Any	Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
		Severe	>3xULN	Any	

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

Neuropathic pain and/or peripheral neuropathy:

Table 7: Dose modifications for bortezomib related neuropathy

Severity of neuropathy	Dose Modification
Grade 1(asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce dose to 1mg/m^2
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
Grade 4 and/or severe autonomic neuropathy	Discontinue treatment
Grade 1: Asymptomatic; clinical or diagnostic observations only Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living (ADL) Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated Grading based on NCI Common Toxicity Criteria CTCAE v 4	

Table 8: Dose Modification of Bortezomib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 3 Non-haematological toxicity	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at the next lower dose level 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.
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue treatment.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Daratumumab: Minimal (**Refer to local policy).**
Bortezomib: Low (**Refer to local policy).**

PRE AND POST INJECTION MEDICATIONS:

- Pre-dose medications consisting of corticosteroid, anti-pyretic and anti-histamines should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every dose of daratumumab as suggested in table 9.
- When dexAMETHasone is the background-regimen specific corticosteroid, the dexAMETHasone treatment dose will instead serve as pre-medication on daratumumab dosing days. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on daratumumab dosing days when patients have received dexamethasone as a pre-medication.
- Consider use of montelukast 10mg PO 60 minutes pre-daratumumab before the first dose only to reduce the incidence of infusion-related reactions
- See other supportive care for recommended post-infusion medications

Table 9: Suggested medications for pre and post daratumumab administration

Day	Drugs	Dose	Route	Timing	Cycle
1,2,8,9	DexAMETHasone	**Refer to Table 1: Treatment table for daratumumab, bortezomib and dexamethasone**[a]			1-3
15	DexAMETHasone	20mg	PO	1-3 hours prior to daratumumab infusion	1-3
16	DexAMETHasone	20mg	PO		1-3
1,2	DexAMETHasone	**Refer to Table 1: Treatment table for daratumumab, bortezomib and dexamethasone**[a]			4-8
1	DexAMETHasone	12mg	PO	1-3 hours prior to daratumumab infusion	From cycle 9 onwards
2,3	DexAMETHasone	4mg	PO		From cycle 9 onwards
1, 8, 15	Paracetamol	1g	PO	1-3 hours prior to daratumumab infusion	Cycles 1-3
1	Paracetamol	1g	PO	1-3 hours prior to daratumumab infusion	Cycle 4 onwards
1, 8, 15	Chlorphenamine[b]	4mg	PO	1-3 hours prior to daratumumab infusion	Cycles 1-3
1	Chlorphenamine[b]	4mg	PO	1-3 hours prior to daratumumab infusion	Cycle 4 onwards

[a] **Note. On the days of daratumumab administration, the scheduled treatment dose of dexAMETHasone will be administered as a premedication prior to infusion**
[b]Or equivalent oral or intravenous antihistamine

OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation. (**Refer to local policy**).
- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Tumour lysis syndrome prophylaxis (**Refer to local policy**).
- H_2 antagonist or proton pump inhibitor (**Refer to local policy**).
- Consider PJP prophylaxis (**Refer to local policy**).
- Influenza vaccination in appropriate patients
- Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.
- **Recommended post-infusion medications for patients with a history of obstructive pulmonary disorder**
    - The use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. 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

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Daratumumab:

- **Interference 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. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask 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. Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.
  In the event of a planned transfusion, blood transfusion centres should be notified of this interference with indirect antiglobulin tests. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.
- **Interference with determination of Complete Response:** Daratumumab is a human IgG kappa monoclonal antibody that can be detected 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 some patients with IgG kappa myeloma protein.
    - Consider use of daratumumab-specific IFE reflex assay (DIRA) to distinguish the therapeutic from the patient's M protein. The DIRA assay can be used to determine whether additional testing, including determination of the sFLC ratio and BM evaluation, is warranted in patients with IgG-κ

band and low measurable M protein (≤2 g/L) to assess the presence of (stringent) CR.

- **Hepatitis B Reactivation:** Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with daratumumab. HBV screening should be performed in all patients before initiation of treatment with daratumumab. For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of daratumumab treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated. In patients who develop reactivation of HBV while on daratumumab, suspend treatment with daratumumab and institute appropriate treatment. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV".

Bortezomib:

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.
- **Hepatic Impairment;** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.
- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore, platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25 x 10^9/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.
- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
- **Renal Impairment:** Patients with renal impairment should be monitored closely.

dexAMETHasone

- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:

- No interaction studies have been performed with daratumumab.
- Additive hypotensive effect with anti-hypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of anti-hypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medications.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Educational materials- HCP
HCP card
https://www.hpra.ie/img/uploaded/swedocuments/cbd1526c-16f6-418c-89bf-da162d5425d9.pdf
Lab card
https://www.hpra.ie/img/uploaded/swedocuments/8e37ebbd-5b08-46a9-9a80-53cc2e1b38ee.pdf

Educational materials – patient:
Patient card
https://www.hpra.ie/img/uploaded/swedocuments/7d6eb084-c129-4b5f-b919-988078d235c9.pdf

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Version	Date	Amendment	Approved By
1	24/09/2020		NCCP Plasma Cell Disorder CAG
2	04/02/2021	Updated to clarify the use of an oral steroid post daratumumab dosing when treatment dexamethasone dose is reduced to 20mg/week	NCCP Plasma Cell Disorder CAG
3	20/09/2021	Regimen review Update of premedication table in supportive care to include recommended pre and post injection medications	NCCP Plasma Cell Disorder CAG
4	20/11/2023	Updated pre-medications table. Amended renal dose modifications for bortezomib as per recommendations by Krens et al 2019	NCCP Plasma Cell Disorder CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.