National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: July 2018

# Daratumumab in addition to bortezomib, thalidomide and dexamethasone for newly diagnosed multiple myeloma

NIHRIO (HSRIC) ID: 12261 NICE ID: 9407

## LAY SUMMARY

Multiple myeloma (MM) is a rare, incurable cancer of the plasma cells in the bone marrow. Bone marrow is the spongy tissue found at the centre of some bones, which produces blood cells for the body. Plasma cells are normally produced in a controlled way, but in cases of MM, large amounts of abnormal plasma cells are produced. These fill the bone marrow and interfere with the production of other cells, including red and white blood cells and platelets. The cause of MM is unknown. Symptoms of MM vary but may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections.

Daratumumab in addition to current licenced treatments (bortezomib, thalidomide and dexamethasone) is in development for adult patients with MM who are newly diagnosed and eligible for high dose chemotherapy and stem cell transplant. Daratumumab is an antibody that inhibits the growth of the abnormal cells in MM and is already being used either alone or in combination with other therapies to treat some specific types of MM. The addition of daratumumab to bortezomib, thalidomide and dexamethasone may provide an alternative treatment option to lower the risk of disease progression or death in newly diagnosed MM patients.



*This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.*

## TARGET GROUP

Multiple myeloma (newly diagnosed adults, high-dose chemotherapy and autologous stem cell transplant eligible) – in combination with bortezomib, thalidomide and dexamethasone

## TECHNOLOGY

### DESCRIPTION

Daratumumab (Darzalex) is an immunoglobulin G, subclass 1, κ light chain (IgG1κ) human monoclonal antibody (mAb) that binds to the cluster of differentiation 38 (CD38) protein expressed at a high level on the surface of multiple myeloma (MM) tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.[1] Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumour cells. Studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38.[2]

Daratumumab in addition to current treatment option (bortezomib, thalidomide and dexamethasone) is in development for adult patients with newly diagnosed MM who are eligible for high-dose chemotherapy and autologous stem cell transplant. In the phase III clinical trial (NCT02541383), participants receive 4 cycles (approximately 4 weeks/cycle) of bortezomib, thalidomide and dexamethasone plus daratumumab 16mg/kg induction therapy followed by autologous stem cell transplantation. This is followed by 2 cycles of bortezomib, thalidomide and dexamethasone plus daratumumab 16 mg/kg consolidation for a total period of 6 cycles spread over 30 weeks.[3]

Daratumumab is currently indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. It is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy. The most frequent adverse events (> 20%, any grade) in MM patients treated with daratumumab were infusion reactions, fatigue, nausea, diarrhoea, muscle spasms, pyrexia, cough, dyspnoea, neutropenia, thrombocytopenia and upper respiratory tract infection.[1]

Daratumumab is also in phase III clinical development for the following:[4]

- MM transplant ineligible patients in combination with lenalidomide and low dose dexamethasone
- Relapsed and refractory MM, 1+ prior lines of therapy in combination with pomalidomide plus low dose dexamethasone
- Amyloidosis
- Subcutaneous formulation
- Smoldering MM

Daratumumab in combination with bortezomib, thalidomide and dexamethasone does not currently have Marketing Authorisation in the EU for any indication.[1]

## INNOVATION and/or ADVANTAGES

Despite recent advances in therapy, MM remains an incurable disease, and new approaches that induce long-term tumour regression with little cross-resistance of existing drugs are needed. Immunotherapy, including novel agents such as daratumumab, is a promising area of development. Daratumumab has shown a favourable safety profile as monotherapy in patients with relapsed/refractory MM and also demonstrates significant single-agent activity. Preclinical data supports its use in combination therapy, and if licensed, daratumumab in addition to bortezomib, thalidomide and dexamethasone will offer an additional treatment option for newly diagnosed adults eligible for high dose chemotherapy and autologous stem cell transplant.[5]

## DEVELOPER

Janssen-Cilag Ltd

## PATIENT GROUP

## BACKGROUND

MM is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in disruption of normal bone marrow function, the over-production of monoclonal immunoglobulin and immunosuppression, and osteolysis and end-organ damage.[6] The disease is characterised by cycles of response and progression. With increasing lines of therapy, there is a decreasing duration of response and ultimately development of refractory disease.[7]

The cause of MM is unknown, but is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS). In almost all cases, MM occurs in those who have previously had MGUS. MGUS is characterised by an excess number of protein molecules (immunoglobulins) present in the blood. MGUS does not cause any symptoms and treatment is not required. However, estimates suggest approximately 1 in every 100 people with MGUS go on to develop MM on an annual basis. There is no known way to delay or prevent this development, and ongoing outpatient tests to check for cancer will usually be recommended in conjunction with a MGUS diagnosis. [8]

Additional risk factors for MM include age, gender, and ethnicity. Cases affecting those under 40 years of age are rare, with men more likely to develop the disease than women. MM is twice as common in black populations compared with white and Asian ethnicities. In early stages, MM may not cause any symptoms or complications and may be diagnosed by routine blood or urine tests.[9] Symptoms of MM can include: bone pain (notably in the spine or chest), nausea, constipation, loss of appetite, physical and mental fatigue, frequent infections, reduced kidney function, anaemia, weight loss, weakness or numbness in the lower extremities, and excessive thirst.[10]

MM patients experience a variety of disease-related events and subsequent disability, such as bone destruction leading to pain, height reduction and body shape changes, bone marrow failure, renal failure, immunodeficiency, and the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments.[12] A similar psychosocial burden may be present in caregivers of MM patients, with the role and level of care required evolving

as the disease progresses.[11] Health-related quality of life assessment tools that introduce the patient's perspective into the clinical process via standardized self-reports may add an additional dimension to traditional endpoints in both clinical trials and practice.[12]

## CLINICAL NEED and BURDEN OF DISEASE

In 2015, MM was the 19th most common cancer in the UK with 4,920 new cases in England and Wales (2,835 male and 2,085 female). MM incidence is strongly linked to age, with almost half (45%) of new cases diagnosed in the UK between 2013-2015 presenting in persons aged 75 years and older.[13] MM incidence rates are projected to rise by 11% in the UK between 2014 and 2035, to 12 cases per 100,000 people by 2035.[13,14]

Based on data from 2010-2011, almost half of patients with MM in England and Wales now survive their disease for at least 5 years with a third surviving for 10 years or more.[15] Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), and the adoption of haematopoietic stem cell transplantation.[18]

In 2016-17 NHS England reported 140,645 finished consultant episodes (FCEs) and 136,025 admissions under ICD code C90.0 (MM) resulting in 90,685 FCE bed days. [16] There were 3,079 MM deaths in 2016, accounting for 2% of all cancer mortality in the UK.[17]

The population likely to be eligible to receive daratumumab in combination with bortezomib, thalidomide and dexamethasone could not be estimated from available published sources.

## PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. Multiple myeloma - lenalidomide (maintenance, post autologous stem cell transplantation) (ID475). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Elotuzumab for multiple myeloma (ID966). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Multiple myeloma (newly diagnosed) - lenalidomide (ID474). Expected June 2018.
- NICE technology appraisal. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- NICE technology appraisal. Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). July 2011.
- NICE diagnostic guidance in development. Multiple myeloma and related disorders - Freelite assays (and alternative technologies identified during scoping) for diagnosis in primary care (GID-DT28). Expected date of issue to be confirmed.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.

### NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

## OTHER GUIDANCE

- UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017[18]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017[19]
- International Myeloma Working Group (IMWG). Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015[20]
- Haemato-oncology Task Force of the British Committee for Standards in Hameatology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014[21]
- European Myeloma Network. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014[22]

## CURRENT TREATMENT OPTIONS

The introduction of the novel agents, thalidomide, bortezomib and lenalidomide as part of the frontline induction both in transplant and non-transplant MM candidates, have markedly improved the anti-myeloma efficacy of the different therapeutic regimens and improved patients' prognosis. Current treatment goals are aimed to further improve the rate of complete remission, time to progression, progression-free survival and overall survival without increasing toxicity.[23] The health and treatment of MM patients is complex, reflecting the effects of the disease, other comorbidities, frailty and the ageing process. MM treatments also have side effects, which may involve permanent organ damage.[18]

In evaluating the right time to initiate treatment of MM patients, clinicians should clearly define the stage of the disease, as well as biologic risk factors and an individual patient's disposition. The IMWG traditionally recommended starting treatment if a newly diagnosed MM patient presented with symptomatic disease as defined by end-organ damage using the so-called CRAB criteria: hyper**C**alcemia, **R**enal insufficiency, **A**nemia, and **B**one disease, and/or the presence of any other clinically significant organ dysfunctions such as an increased occurrence of infections, the development of paraprotein-related polyneuropathy, etc.[20, 24]

While transplant-eligible MM patients typically receive a triplet induction therapy followed by autologous transplantation and, in some jurisdictions, lenalidomide maintenance, other therapeutic elements (e. g. other maintenance strategies, consolidation, tandem transplantation and etc.) have to be decided on an individualized appraisal of risk and toxicities. [24,25] In the management of newly diagnosed MM, bortezomib is recommended by NICE as an option within its marketing authorisation. That is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.[26]

## EFFICACY and SAFETY

| | |
|---|---|
| **Trial** | Cassiopeia, NCT02541383; Part 1 - bortezomib + thalidomide + dexamethasone vs. daratumumab in combination with bortezomib + thalidomide + dexamethasone; Part 2 – observation vs. daratumumab; phase III |
| **Sponsor** | Janssen-Cilag Ltd |
| **Status** | Ongoing |
| **Source of Information** | Trial registry[3] |
| **Location** | 4 EU countries (not including UK) |
| **Design** | Randomised, open-label, 2-arm |
| **Participants** | n=1080 (planned); aged 18-65 years; previously untreated MM; eligible for high dose chemotherapy and autologous stem cell transplantation; Eastern Cooperative Oncology Group performance status score of 0, 1 or 2 |
| **Schedule** | Participants are randomized to one of 2 treatment groups:<br>• **Arm A – Part 1**: 4 cycles of bortezomib, thalidomide and dexamethasone induction therapy, followed by autologous stem cell transplantation, followed by 2 cycles of bortezomib, thalidomide and dexamethasone consolidation.<br>• **Arm B – Part 1:** 4 cycles of bortezomib, thalidomide and dexamethasone plus daratumumab 16mg/kg induction therapy, followed by autologous stem cell transplantation, followed by 2 cycles of bortezomib, thalidomide and dexamethasone plus daratumumab 16 mg/kg consolidation<br><br>All responders will then be re-randomized to one of 2 treatment groups:<br>• **Arm A – Part 2:** Observation (no treatment)<br>• **Arm B – Part 2:** Maintenance treatment with daratumumab 16mg/kg every 8 weeks for 2 years<br><br>The study will include a 28-day screening phase, a treatment phase of 6 treatment cycles (each cycle is 4 weeks in duration for total period of 30 weeks), and a follow up phase of 2 years. The total duration for each participant in the study will be approximately 138 weeks. |
| **Follow-up** | Follow up phase of 2 years |
| **Primary Outcomes** | • stringent Complete Response (sCR) after consolidation therapy [Time frame: Up to 9 months]<br>sCR is defined by achieving CR (complete response) in addition to having a normal serum FLC (Free Light Chain) ratio and absence of clonal cells in bone marrow<br><br>• Progression free survival (PFS) after maintenance therapy [Time Frame: up to 60 months]<br>Time from the date of second randomization to either progressive disease (PD) or death |
| **Secondary Outcomes** | • PFS (from first randomization) [Time frame: Up to 60 months]<br>Time from the initial randomization to either PD or death<br><br>• Time to Progression (TTP) [Time frame: Up to 60 months ] |

| | |
|---|---|
| | Time from the initial randomization to confirmed PD or death due to progressive disease<br><br>• Proportion of Post Autologous Stem Cell Transplantation (ASCT)/ consolidation CR rate [Time frame: Up to 9 months]<br>Proportion of participants who have achieved CR or sCR by the end of consolidation treatment<br><br>• Proportion of post ASCT/consolidation Minimal Residual Disease (MRD) negativation [Time frame: Up to 9 months]<br>Proportion of participants who have achieved MRD negative status by the end of consolidation<br><br>• Proportion of post induction sCR [Time frame: Up to 4 months]<br>Proportion of participants who have achieved sCR prior to high-dose therapy/ASCT<br><br>• PFS 2 (from first randomization) [Time frame: Up to 60 months]<br>Time from initial randomization to subsequent progression on next-line of therapy after disease progression on study treatment<br><br>• OS (overall survival) (from first randomization) [Time frame: Up to 60 months]<br>Time from initial randomization to death |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | Estimated study completion date Aug 2024 |

# ESTIMATED COST and IMPACT

## COST

Daratumumab is already marketed in the UK; a 100mg/5ml vial for solution for infusion vials costs £360.00.[27]

Bortezomib is already marketed in the UK; a 3.5 mg powder for solution for injection vials costs £762.38.[28]

Thalidomide is already marketed in the UK; a pack of 30 x 25mg tablets costs £1075.00, and a pack of 28 x 50mg capsules costs £298.48.[29]

Dexamethasone is already marketed in the UK; the cost for 3.3mg/mL, 3.8mg/mL or 6.6mg/2mL for injection ampoules varies from £12.00-£24.00, indicative of supplier and unit size.[30]

## IMPACT – SPECULATIVE

## IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ No impact identified

## IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ None identified

## IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other: *uncertain unit cost*

☐ None identified

## OTHER ISSUES

☒ None identified

## REFERENCES


[1] electronic Medicines Compendium (eMC). *Darzalex 20 mg/mL concentrate for solution for infusion.* Available from: https://www.medicines.org.uk/emc/product/7250 [Accessed 26th June 2018]

[2] European Medicines Agency (EMA). *Assessment report: Darzalex*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004077/WC500207295.pdf [Accessed 29th June 2018]

[3] ClinicalTrials.gov. *A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia)*. Available from: https://clinicaltrials.gov/ct2/show/NCT02541383 [Accessed 24th June 2018] Last updated 2nd June 2016

[4] Janssen-Cilag. *Selected Pharmaceuticals in Late Stage U.S. and E.U. development or Registration as of 01/23/18*. Available from: http://www.investor.jnj.com/_document/jnj-pipeline-q4-2017?id=00000161-28af-dbe1-a9e9-2bff4e700000 [Accessed 26th June 2018]

[5] Phipps C, Chen Y, Gopalakrishnan S and Tan D. Daratumumab and its potential in the treatment of multiple myeloma: overview of the preclinical and clinical development. *Therapeutic Advances in Hematology*. 2015; 6(3): 120-127. Available from: https://dx.doi.org/10.1177%2F2040620715572295

[6] Hipp S, Tai YT, Blanset D et al. A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. *Leukemia*. 2017;31: 1743-1751. Available from: https://dx.doi.org/10.1038/leu.2016.388

[7] Borrello I. Can we change the disease biology of multiple myeloma? *Leukemia Research*. 2012;36 Suppl 1:S3–12. Available from: https://doi.org/10.1016/S0145-2126(12)70003-6

[8] NHS. *Multiple myeloma*. Available from: https://www.nhs.uk/conditions/multiple-myeloma/causes/ [Accessed 31st January 2018]. Last updated: 16th February 2015

[9] NHS Direct Wales. *Multiple myeloma*. Available from: http://www.nhsdirect.wales.nhs.uk/encyclopaedia/m/article/multiplemyeloma/ [Accessed 29th June 2018]

[10] The Mayo Clinic. *Multiple myeloma - symptoms*. Available from: https://www.mayoclinic.org/diseases-conditions/multiple-myeloma/symptoms-causes/syc-20353378 [Accessed 31st January 2018] Last updated 15th December 2017

[11] Multiple Myeloma Research Foundation. *Caregiver self-care and financial support*. Available from: https://www.themmrf.org/caregiver-self-care-and-financial-support/ [Accessed 1st February 2018]. Last updated 17th March 2017

[12] Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma – does it matter*? Journal of the European Hematology Association*. 2015;100: 704-705. Available from: http://dx.doi.org/10.3324/haematol.2015.127860

[13] Cancer Research UK. *Myeloma incidence by sex and UK country*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero [Accessed 1st February 2018] Last updated 23rd January 2018

[14] Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *British Journal of Cancer*; 115: 1147-1155. Available from: http://dx.doi.org/10.1038/bjc.2016.304

[15] Cancer Research UK. *Myeloma survival*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Two [Accessed 5th February 2018] Last updated 23rd January 2018

[16] NHS England. *Hospital Admitted Patient Care Activity 2016-17: Diagnosis*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 5th February 2018] Last updated 3rd October 2017

[17] Cancer Research UK. *Myeloma mortality statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/mortality [Accessed 17th July 2018]

[18] Snowden JA, Greenfield DM, Bird JM et al. on behalf of the UK Myeloma Forum (UKMF) and the British society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. *British Journal of Haematology*;2017(176): 888-907. Available from: https://doi.org/10.1111/bjh.14514

[19] American National Comprehensive Cancer Network. *American NCCN guidelines: Version 3 - NCCN Evidence Blocks: Myeloma Therapy*. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma_blocks.pdf Login required

[20] Palumbo A, Avet-Loiseau H, Oliva S et al. on behalf of the International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(26): 2863-2869. Available from: http://dx.doi.org/10.1200/JCO.2015.61.2267

[21] Bird JM, Owen RG, D'Sa S et al. on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Hameatology (BCSH) and UK Myeloma Forum. *Guidelines for the diagnosis and management of Multiple Myeloma*. Available from: https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2014/08/MYELOMA_GUIDELINE_Feb_2014_for_BCSH1.pdf [Accessed 5th February 2018]

[22] Engelhardt M, Terpos E, Kleber M et al. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica* 2014;99: 232–42. Available from: https://doi.org/10.3324/haematol.2013.099358

[23] Cejalvo MJ and de la Rubia J. Clinical treatment of newly diagnosed multiple myeloma. *Expert Review of Hematology*. 2015; 8(5): 595-611. Available from: https://doi.org/10.1586/17474086.2015.1078236

[24] Willenbacher E, Balog A, and Willenbacher W. Short overview on the current standard of treatment in newly diagnosed multiple myeloma. *memo – Magazine of European Medical Oncology*. 2018; 11(1): 59-64. Available from: https://doi.org/10.1007/s12254-018-0383-3

[25] Syed YY. Lenalidomide: A Review in Newly Diagnosed Multiple Myeloma as Maintenance Therapy After ASCT. *Drugs*. 2017; 77(13): 1473-1480. Available from: https://doi.org/10.1007/s40265-017-0795-0

[26] National Institute for Health and Care Excellence (NICE). *Myeloma: diagnosis and management [NG35]*. Available from: https://www.nice.org.uk/guidance/ng35

[27] British National Formulary (BNF). *Daratumumab*. Available from: https://bnf.nice.org.uk/medicinal-forms/daratumumab.html [Accessed 26th June 2018]

[28] British National Formulary (BNF). *Bortezomib*. Available from: https://bnf.nice.org.uk/medicinal-forms/bortezomib.html [Accessed 26th June 2018]

[29] British National Formulary (BNF). *Thalidomide*. Available from: https://bnf.nice.org.uk/medicinal-forms/thalidomide.html [Accessed 26th June 2018]

[30] British National Formulary (BNF). *Dexamethasone*. Available from: https://bnf.nice.org.uk/medicinal-forms/dexamethasone.html [Accessed 26th June 2018]