Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Daratumumab (subcutaneous injection) for multiple myeloma

NIHRIO ID	21697	**NICE ID**	10063
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	648226

Licensing and market availability plans	Currently in pre-registration.

SUMMARY

Daratumumab injected under the skin (subcutaneous formulation) is in development for the treatment multiple myeloma (MM) as an alternative to currently approved daratumumab intravenous formulation. MM is a rare, incurable cancer of the plasma cells in the bone marrow where large amounts of abnormal plasma cells are produced and interfere with the production of platelets, red and white blood cells. People with MM will experience periods of time without symptoms followed by periods when the illness comes back ('relapsed' MM). Eventually the periods without symptoms will shorten and the illness will become immune to the drugs given to treat it ('refractory' MM).

Daratumumab is a type of immune therapy that acts by inhibiting the growth of cancer cells in MM. The intravenous formulation of daratumumab is already licensed in the UK for the treatment of MM. Subcutaneous administration of daratumumab may make it possible for patients to receive this emerging therapy more easily, safely (with lower rates of infusion reaction) and conveniently (with only a 3 to 5 minute administration versus several hours for the infusion formulation). If licensed, this new formulation has the potential to replace the existing intravenous route of administration while contributing to reduced healthcare costs and greater patient convenience.

PROPOSED INDICATION

Multiple myeloma (MM).[a]

TECHNOLOGY

DESCRIPTION

Daratumumab (Darzalex) is an IgG1κ human monoclonal antibody (mAb) that binds to the 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. Based on in vitro studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These 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. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab mediated cell lysis.[1]

Daratumumab monotherapy as a subcutaneous injection is in development for the treatment of adult patients with relapsed or refractory MM who have received at least three previous lines of treatment including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease is refractory to both a PI and an IMiD.[2] In the phase III clinical trial (COLUMBA; NCT03277105) participants receive a fixed dose of daratumumab as 1800 milligram (mg) subcutaneously (Dara SC) co-formulated with recombinant human hyaluronidase (rHuPH20) 2000 Unit per millilitre (U/mL), once weekly in Cycle 1 and 2, every 2 weeks in Cycle 3 to 6, every 4 weeks in Cycle 7 and thereafter until disease progression, unacceptable toxicity or the end of study. The duration for each cycle is 4 weeks.[2,3]

INNOVATION AND/OR ADVANTAGES

Results from the phase I trial PAVO study show that subcutaneous delivery of daratumumab offered consistent efficacy with shorter infusion times and lower risk of infusion reactions, which may benefit patients, physicians and healthcare systems alike. Subcutaneous administration of daratumumab could make it possible for more patients to receive this emerging therapy more easily for advanced or recently diagnosed MM.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daratumumab (subcutaneous administration) does not currently have Marketing Authorisation in the EU/UK for any indication.

Daratumumab (by intravenous infusion) has the following therapeutic indications;

- for the treatment of relapsed and refractory multiple myeloma (as monotherapy after failure of a proteasome inhibitor and an immunomodulatory agent);

[a] Information provided by Janssen-Cilag Ltd on UK PharmaScan

- in combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant;
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.[6,7]

Daratumumab (subcutaneous administration) is in phase III clinical development for smouldering MM.[8] Daratumumab (subcutaneous administration) is also in phase III clinical development for front line transplant eligible (Perseus / MMY3014 / NCT02874742) and transplant ineligible (Cepheus / MMY3019/ NCT03277105) indications.[2,9]

Daratumumab received European Orphan Designation for the treatment of plasma cell myeloma in July 2013.[10]

PATIENT GROUP

DISEASE BACKGROUND

MM is an incurable orphan disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, and immunosuppression, as well as osteolysis and end-organ damage.[11] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[12] Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[13]

The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities.[14] MM 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.[15] MGUS is characterised by an excess number of 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, and sub-classifications of MGUS have allowed identification of patients with much higher rates of progression to frank MM. 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.[15]

In the early stages of the condition, MM may not present any symptoms or complications and may be diagnosed by routine blood or urine tests such as an abnormal elevation in serum immunoglobulin levels.[11] Other features of MM are often denoted by the "CRAB" criteria, which can include hyperCalcemia, Renal dysfunction, Anaemia and Bone disease. Symptoms associated with these CRAB criteria 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, loss of muscle control in the lower extremities, and excessive thirst.[13,16]

Therapeutic interventions may also produce troublesome side effects and functional impairments. 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. Health-related quality of life assessment tools that introduce the patient's perspective into the clinical process via standardised self-reports may add an additional dimension to traditional endpoints in both clinical trials and practice.[17]

CLINICAL NEED AND BURDEN OF DISEASE

The estimated European prevalence of MM is 11.9 per 100,000.[18] As per 2015, myeloma was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[19]

In England in 2016, there were a total of 4,731 (2,706 in men and 2,025 in women) registrations of multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C90) with an European age-standardised rate of 11.7 per 100,000 in men and 7.4 per 100,000 in women.[20] In the same year and territory, there were 2,606 registrations of death due to myeloma and malignant plasma cell neoplasms (ICD-10 code C90) with an European age-standardised rates per 100,000 equal to 6.4 and 4.2 for men and women respectively.[20] Myeloma is projected to rise from 5,500 cases (11.12 per 100,000) in 2014 to 8888.01 (12.38 in 100,000) in 2035.[21]

Almost half of patients with MM in England and Wales survive their disease for at least 5 years, with a third surviving for 10 years or more (2010-2011).[22] Increased life expectancy is mainly due to the availability of novel therapeutic agents described above including IMiDs and PIs, and the adoption of haematopoietic stem cell transplantation as well as earlier diagnosis and improved supportive care.[23]

In 2017-18, NHS England reported 139,605 finished consultant episodes (FCEs) and 134,697 admissions under ICD code C90.0 (multiple myeloma and malignant plasma cell neoplasms) resulting in 96,137 FCE bed days.[24]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Despite recent progress, MM remains incurable and the vast majority of patients will progress on available agents and require treatment with novel therapies. 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. Periods of stability followed by relapse are typical, although the increasing use of consolidation and maintenance results in many patients on treatment for prolonged periods of time during disease stability.[25]

The choice of treatment at relapse should consider the balance between efficacy and toxicity of the treatment schedule, disease related factors such as risk stratification of the disease, prior drug therapy and the patients' response to prior treatment. The length of the prior remission duration is a critical component in making a choice of salvage therapy. The depth of the first response, remission duration of the patient's prior therapies, and tumour burden at relapse can suggest the aggressiveness of the relapse.[26]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of possible sequences of treatments for relapsed or refractory MM:[27-29]

- Ixazomib, with lenalidomide and dexamethasone, is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults only if they have already had 2 or 3 lines of therapy and the conditions in the managed access agreement for ixazomib are followed.
- Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies. The drug cost of lenalidomide (excluding any related costs) for people who

remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer.

- Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma, that is, for 'adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent' when the company provides panobinostat with the discount agreed in the patient access scheme.
- Daratumumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed and refractory multiple myeloma in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies and the conditions in the managed access agreement are followed.
- Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.
- Bortezomid is recommended for use in relapse MM patients.
- Carfilzomib is recommended for use in relapse MM patients who did not receive bortezomib at front line.

PLACE OF TECHNOLOGY

If licensed, daratumumab subcutaneous formulation could potentially replace the currently licensed intravenous formulation for the treatment of patients with relapsing or refractory multiple myeloma that have received at least 3 prior lines of therapy.

CLINICAL TRIAL INFORMATION

Trial	**COLUMBA, NCT03277105, EudraCT 2017-000206-38; adults aged older than 18 years; daratumumab subcutaneous vs daratumumab intravenous; phase III.**
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Abstract, [3] trial registry[2,30]
Location	EU (inc UK), USA, and other countries
Design	Randomised, active-controlled, parallel assignment
Participants	n=480 (planned); aged 18 and over; with RRMM must have received ≥3 prior lines of therapy, including a proteasome inhibitor (PI; ≥2 cycles or 2 months of treatment) and an immunomodulatory drug (IMiD; ≥2 cycles or 2 months of treatment), or must be double refractory to both a PI and an IMiD.
Schedule	Randomised to: • Fixed dose of daratumumab as 1800 milligram (mg) subcutaneously (Dara SC) co-formulated with recombinant human hyaluronidase (rHuPH20) 2000 Unit per millilitre (U/mL), once weekly in Cycle 1 and 2, every 2 weeks in Cycle 3 to 6, every 4 weeks in Cycle 7 and thereafter until disease progression, unacceptable toxicity or the end of study. The duration for each cycle is 4 weeks. • Daratumumab for intravenous infusion (Dara IV) 16 mg/kg by once weekly in Cycle 1 and 2, every 2 weeks in Cycle 3 to 6, every 4 weeks at Day 1 in Cycle 7 and thereafter until disease progression, unacceptable toxicity or the end of study.

Follow-up	Active treatment for 7 cycles (28 weeks), follow-up 18 months
Primary Outcomes	1. Overall Response Rate (ORR) [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years)] 2. Maximum Trough Concentration (Ctrough) of Daratumumab [Time Frame: Cycle 3 (each cycle 28 days) Day 1]
Secondary Outcomes	1. Percentage of participants With Infusion-Related Reactions (IRR) [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years)] 2. Progression-Free Survival (PFS) [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 3. Very Good Partial Response (VGPR) or Better Rate [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 4. Complete Response (Including sCR) or Better Rate [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 5. Time to Next Treatment [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 6. Overall Survival (OS) [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 7. Patient-Reported Satisfaction With Therapy [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 8. Duration of Response [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)] 9. Time to response [Time Frame: At 6 months after 480 participants have been randomized (approximately 2 years) and 18 months after the last participant randomized (approximately 3 years)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as Nov 2019, study completion date reported as Oct 2020.

Trial	**CR108435, NCT03412565, EudraCT 2017-004203-41; daratumumab SC in combination with standard multiple myeloma (MM) regimens; phase II.**
Sponsor	Janssen Research & Development, LLC
Status	Ongoing
Source of Information	Trial registry[31]
Location	EU (inc UK), USA, and other countries
Design	Non-randomised, active-controlled, parallel assignment
Participants	n=(199); Multiple myeloma diagnosed according to the International Myeloma Working Group (IMWG) diagnostic criteria.

Schedule	• Arm 1: Daratumumab (D)+Bortezomib+Lenalidomide+Dexamethasone (D-VRd). Participants will receive daratumumab 1800 milligram (mg) by subcutaneous (SC) injection on Days 1, 8 and 15 of Cycles 1 to 3 (each cycle of 21 days) and on Day 1 of Cycle 4; bortezomib 1.3 milligram per square meter (mg/m^2) SC injection on Days 1, 4, 8 and 11 of Cycles 1 to 4; lenalidomide 25 mg orally on Day 1 through Day 14 of Cycles 1 to 4 and dexamethasone 20 mg orally or intravenously on Days 1, 2 ,8, 9, 15 and 16 of Cycle 1 to 4. • Arm 2: D + Bortezomib + Melphalan + Prednisone (D-VMP). Participants will receive daratumumab 1800 mg by SC injection on Days 1, 8, 15 and 22 of Cycles 1 and 2 then on Day 1 and 15 of Cycles 3 to 6 and on Day 1 of Cycle 7 and thereafter until documented progression of disease, unacceptable toxicity, or end of study; lenalidomide 25 mg orally on Day 1 through Day 21 of each cycle until documented progression of disease, unacceptable toxicity, or end of study and dexamethasone 40 mg orally or intravenously weekly until documented progression of disease, unacceptable toxicity, or end of study. • Arm 3: D + Carfilzomib + Dexamethasone (D-Kd). Participants will receive daratumumab 1800 mg by SC injection on Days 1, 8, 15 and 22 of Cycles 1 and 2 (each cycle is of 28 days) then on Day 1 and 15 of Cycles 3 to 6 and on Day 1 of Cycle 7 and thereafter until documented progression of disease, unacceptable toxicity, or end of study; Carfilzomib 20 mg/m^2 intravenously (IV) on Day 1 of Cycle 1 only then 70 mg/m^2 IV on Days 8 and 15 of Cycle 1 and Days 1, 8 and 15 of Cycle 2 and thereafter until documented progression of disease, unacceptable toxicity, or end of study and dexamethasone 40 mg orally or IV weekly for Cycles 1-9 then on Days 1, 8, 15 of each cycle for Cycles 10 and thereafter until documented progression of disease, unacceptable toxicity, or end of study.
Follow-up	Approximately 2.5 years
Primary Outcomes	1. D-VMP, D-Kd, and D-Rd Cohort: Overall Response Rate (ORR) [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)] 2. D-VRd Cohort: Very Good Partial Response (VGPR) or Better Rate [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)]
Secondary Outcomes	1. Maximum Observed Serum Concentrations (Cmax) of Daratumumab [Time Frame: D-VRd: Day 4 of Cycles 1 and 4 and post treatment 30 Days and at week 8; D-VMP and D-Rd: Day 4 of Cycles 1 and 2 and post treatment 30 Days and at week 8; D-Kd: Day 4 of Cycles 1 and 3 and post treatment 30 Days and at week 8] 2. Minimum Observed Serum Concentrations (Cmin) of Daratumumab [Time Frame: D-VRd: predose on Day 1 of Cycles 1, 3, and 4; D-VMP: predose on Day 1 of Cycles 1, 2, 3, 6 and 9; D-Rd: predose on Day 1 of Cycles 1, 3, 6, 9 and 12 and D-Kd: predose on Day 1 of Cycles 1, 3, 6, 9, and 12] 3. Percentage of Participants with Infusion-Related Reactions (IRR) [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)] 4. D-Kd, D-VMP, and D-Rd Cohort: Very Good Partial Response (VGPR) or Better Rate [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)]

	5. D-VRd Cohort: Overall Response Rate (ORR) [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)] 6. Complete Response or Better Rate [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)] 7. Duration of Response (DOR) [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)] 8. Number of Participants with Anti-Drug Antibodies Against Daratumumab or Recombinant Human Hyaluronidase (rHuPH20) [Time Frame: Up to 8 weeks after the last dose of study drug (approximately 1 year)] 9. D-Kd, D-VMP, and D-Rd Cohorts: Percentage of Participants who are Minimal Residual Disease (MRD) Negative [Time Frame: 18 months after the last participant enrolled (approximately 2.5 years)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as September 2019, final study completion date February 2021.

ESTIMATED COST

The cost of daratumumab subcutaneous formulation is not yet known. The NHS indicative price for daratumumab 20 mg per 1 ml (Darzalex 100mg/5ml concentrate solution for infusion vials) is £360.00.[6]

ADDITIONAL INFORMATION

Janssen-Cilag Ltd. has indicated that this licence is an alternative to the current IV formulation across all current and future licensed daratumumab indications.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating multiple myeloma after 3 or more therapies (ID1535). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma (ID974). Expected date of issue to be confirmed.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Daratumumab with lenalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA454). July 2017.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.

- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). June 2009. Last updated April 2014.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE clinical guideline. Metastatic malignant disease of unknown primary origin in adults: diagnosis and management (CG104). July 2010.
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NHS ENGLAND (POLICY/COMMISSIONING) 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.

OTHER GUIDANCE

- 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. 2017.[23]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017.[32]
- Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[33]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015.[34]
- The Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014.[35]

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