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HEALTH TECHNOLOGY BRIEFING
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Daratumumab in addition to bortezomib, lenalidomide and dexamethasone for multiple myeloma – first line

NIHRIO ID	27120	**NICE ID**	10305
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	652034

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Daratumumab in addition to bortezomib, lenalidomide and dexamethasone is in clinical development for newly diagnosed multiple myeloma (MM). MM is a rare, incurable cancer of the plasma cells (a type of white blood cells) in the bone marrow (the spongy tissue at the centre of some bones) where large amounts of abnormal plasma cells are produced and interfere with the production of red and white blood cells and platelets. The current first line treatment is high dose chemotherapy followed by autologous stem cell transplant. Autologous stem cell transplant is a procedure where a patient's healthy stem cells are collected and given back after treatment but due to frailty or comorbidities some patients are ineligible and require other treatment options.

Daratumumab is a type of immune therapy that is administered subcutaneously and acts by inhibiting the growth of cancer cells in MM via a surface protein called CD38. If licenced it is hoped daratumumab in addition to bortezomib, lenalidomide and dexamethasone could provide better long term outcomes for patients with newly diagnosed multiple myeloma who are ineligible for high-dose chemotherapy with autologous stem cell transplant.

PROPOSED INDICATION

Newly diagnosed multiple myeloma in adults who are previously untreated and for whom autologous stem cell transplant is not planned as initial therapy.[1]

TECHNOLOGY

DESCRIPTION

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma 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. 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.[2]

Daratumumab in addition to bortezomib, lenalidomide and dexamethasone is currently in clinical development for the treatment of newly diagnosed multiple myeloma in adults who are ineligible for high-dose chemotherapy with autologous stem cell transplant. In the phase III trial (NCT03652064), daratumumab 1800 mg was administered via subcutaneous (SC) injection once a week for cycles 1 and 2 (21 days per cycle), then once every 3 weeks for cycles 3 through 8 and then once every 4 weeks for cycle 9 and beyond until disease progression or unacceptable toxicity. Bortezomib 1.3 mg/m^2 was administered via SC injection twice weekly on days 1, 4, 8 and 11 for cycles 1 through 8. Lenalidomide 25 mg was administered orally on day 1 to day 14 for cycles 1 through 8 and on day 1 to day 21 for cycle 9. Dexamethasone 20 mg was administered orally or through intravenous (IV) infusion on days 1, 2, 4, 5, 8, 9, 11, 12 for cycles 1 through 8 and 40 mg on days 1, 8, 15 and 22 during cycle 9 and beyond followed by daratumumab-lenalidomide-dexamethasone (DRd) until disease progression or unacceptable toxicity.[1]

INNOVATION AND/OR ADVANTAGES

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone simultaneously is a new combination for multiple myeloma which is being investigated for both front-line transplant eligible (NCT03710603, NCT02874742) and ineligible patients (NCT03652064).[3] Additionally, the rationale for this techonology was to utilize the SC formulation of daratumumab instead of the IV formulation, which provides similar exposure and limits additional toxicity to participants, treated with this quadruplet regimen.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone is not licensed for any cancer indications in the EU/UK.

Daratumumab is currently licensed in the UK for the following indications:[2]

- in combination with lenalidomide and dexamethasone or 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 bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible 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
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Bortezomib is currently licensed in the UK for the following indications:[4]

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation (HSCT)
- in combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with HSCT
- in combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with HSCT
- in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for HSCT.

Lenalidomide is currently licensed in the UK for the following indications:[5]

- as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation
- as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant
- In combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy
- as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate
- as monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma
- in combination with rituximab (anti-CD20 antibody) for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

Dexamethasone is licensed as palliative treatment in many cancer indications as well as being used in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction.[6]

The common adverse events (affecting at least 1 in 10 patients) for daratumumab include: pneumonia, bronchitis, upper respiratory tract infection, neutropenia, thrombocytopenia, anaemia, lymphopenia, leukopenia, decreased appetite, peripheral sensory neuropathy, paraesthesia, headache, hypertension, cough, dyspnoea, diarrhoea, constipation, nausea,

vomiting, back pain, muscle spasms, fatigue, peripheral oedema, pyrexia, asthenia, and infusion-related reaction.[2]

Common adverse events for bortezomib include: thrombocytopenia, neutropenia, anaemia, decreased appetite, neuropathies, peripheral sensory neuropathy, dysaesthesia, neuralgia, nausea and vomiting symptoms, diarrhoea, constipation, musculoskeletal pain, pyrexia, fatigue and asthenia.[4]

Common adverse events for lenalidomide include: pneumonia, upper respiratory tract infection, neutropenic infection, bronchitis, influenza, gastroenteritis, sinusitis, nasopharyngitis, rhinitis, neutropenia, febrile neutropenia, thrombocytopenia, anaemia, leucopenia, lymphopenia, hypokalaemia, paraesthesia, cough, diarrhoea, constipation, abdominal pain, nausea, rash, dry skin, muscle spasms, fatigue, asthenia and pyrexia.[5]

In July 2013, orphan designation was granted by the European Commission for daratumumab for the treatment of plasma-cell myeloma.[7]

PATIENT GROUP

DISEASE BACKGROUND

MM is a type of bone marrow cancer that is 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.[8,9] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[10]

The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities. MM is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS).[9] Additional risk factors for MM include age, gender, and ethnicity. The risk of MM increases with age with most people diagnosed in their mid-60s. Men are more likely to develop the disease than women and MM is twice as common in black populations compared with white.[11]

In early stages, MM may not cause any symptoms or complications and can be diagnosed by routine blood or urine tests. Eventually, myeloma causes a wide range of problems, which can include bone fracture, tenderness or pain, anaemia, fatigue, kidney problems or infections or less commonly bruising and unusual bleeding.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017 myeloma was the 19th most common cancer in the UK accounting for 2% of all new cancer cases.[12] In England, in 2017 there were 5,034 newly diagnosed cases of multiple myeloma and malignant plasma cell neoplasms (ICD-10: C90). Incidence is strongly linked to age, with the highest rates in people aged 70 to 74years.[13] Over the last decade, incidence rates have increased by a seventh (15%) represented by an increase in males of 17% and 10% for females. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[12]

In England in 2018-19 there were 142,827 finished consultant episodes and 137,870 hospital admissions with a primary diagnosis of MM (ICD-10 code C90.0), resulting in 89,190 bed days and 126,115 day cases.[14] In England, 82.7% of people diagnosed with myeloma survive their disease for 1 year (age-standardised), with a 52.3% surviving for 5 years (2013-17).[15] In

England in 2018, there were 2,697 registrations of death where MM was recorded as the underlying cause.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

At diagnosis patients may not experience symptoms (also known as smoldering multiple myeloma) and may not require treatment. Doctors will regularly monitor patients for disease progression with periodic blood and urine tests. Initial treatment for those not considered eligible for bone marrow transplant (based on frailty and performance status measure) include chemotherapy combined with corticosteroids, targeted therapy or biological therapy.[17]

CURRENT TREATMENT OPTIONS

For the first-line treatment of newly diagnosed myeloma for whom stem cell transplantation is considered inappropriate NICE recommends:[18]

- Thalidomide in combination with an alkylating agent and a corticosteroid
- Bortezomib in combination with an alkylating agent and a corticosteroid if the person is unable to tolerate or has contraindications to thalidomide.
- Lenalidomide plus dexamethasone if the person is unable to tolerate or has contraindications to thalidomide.[19]

PLACE OF TECHNOLOGY

If licenced daratumumab in addition to bortezomib, lenalidomide and dexamethasone could provide another first line treatment option for patients with newly diagnosed multiple myeloma who are ineligible for high-dose chemotherapy with autologous stem cell transplant.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT03652064, 2018-001545-13; A Phase 3 Study Comparing Daratumumab, VELCADE (Bortezomib), Lenalidomide, and Dexamethasone (D-VRd) With VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy **Phase III -** Active, not recruiting **Location:** EU countries (inc UK), United States, Canada, and other countries. **Primary completion date:** October 2020
Trial design	Randomised, open label, parallel assignment.
Population	N= 395; aged 18 and older; diagnosis of multiple myeloma.
Intervention(s)	Participants will receive SC injection of daratumumab and bortezomib, oral lenalidomide and dexamethasone followed by daratumumab-lenalidomide-dexamethasone (DRd) until disease progression or unacceptable toxicity.
Comparator(s)	Same protocol without daratumumab.
Outcome(s)	Primary outcome(s):

	• Percentage of Participants with Negative Minimal Residual Disease (MRD) Status [Time Frame: After randomization and prior to progressive disease (PD) or the start of subsequent anti-myeloma therapy approximately 2.5 years] See trial for the full list.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price for daratumumab is:[20]

- Darzalex 100mg/5ml concentrate for solution for infusion vials £360.00 (Hospital only)
- Darzalex 400mg/20ml concentrate for solution for infusion vials £1440.00 (Hospital only).

New formulation also available in the UK:[21]

- Darzalex subcutaneous formulation with recombinant human hyaluronidase PH20 1,800 mg solution, packsize 1x15ml vial £4,320.

The NHS indicative price for bortezomib is:[22]

- Bortezomib 3.5mg/1.4ml solution for injection vials £495.55 and powder for solution for injection: £217.82 (1mg), £544.56 (2.5mg) and £762.38 (3.5mg).

The NHS indicative price for lenalidomide is:[23]

- £3,426.00 for 21x2.5 mg capsules, £3,570.00 for 21x5 mg capsules, £3,675.00 for 21x7.5 mg capsules, £3,780.00 for 21x10 mg capsules, £3,969.00 for 21x15 mg capsules, £4,168.50 for 21x20 mg capsules and £4,368.00 for 21x25 mg capsules.

The NHS indicative price for dexamethasone is:[24]

- Neofordex tablets a pack of 10 x 40 £200.00.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Daratumumab in combination for untreated multiple myeloma when stem cell transplant is unsuitable (ID1492). Expected publication date to be confirmed.
- NICE technology appraisal in development. Ixazomib with lenalidomide and dexamethasone for untreated multiple myeloma (ID1170). Expected publication date to be confirmed.
- NICE technology appraisal. Lenalidomide plus dexamethasone for previously untreated multiple myeloma (TA587). June 2019
- NICE technology appraisal. Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). July 2011.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

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

- NCCN Guidelines Insights: Multiple Myeloma, Version 3. 2018.[25]
- 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.[26]
- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[27]
- 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.[28]

ADDITIONAL INFORMATION

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