Health Technology Briefing
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Daratumumab with bortezomib, lenalidomide and dexamethasone for previously untreated transplant eligible multiple myeloma

Company/Developer	Janssen

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26764	NICE ID: 10300	UKPS ID: 652033

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone is being developed for adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with autologous stem cell transplant (ASCT). Multiple myeloma is an incurable type of cancer which develops when plasma cells inside the bone marrow become cancerous. This results in the excessive and abnormal production of plasma cells that interfere with the production of other cells including the red blood cells and white blood cells. Multiple myeloma can affect several areas of the body and symptoms can include: bone pain; hypercalcaemia; kidney problems; organ damage; and immune issues. Death rate amongst multiple myeloma patients remains high so there is a need to develop additional treatment options for these patients.

Daratumumab is a monoclonal antibody (a type of protein) that is administered to patients via subcutaneous injection. It works by selectively targeting and blocking the action of a protein called CD38 which is expressed on the surface of cancerous plasma cells. Through blocking the action of CD38, daratumumab prevents the growth of cancerous cells expressing CD38, resulting in tumour cell death. If licenced, daratumumab in combination with bortezomib, lenalidomide and dexamethasone will offer an additional treatment option for multiple myeloma patients who are eligible for high-dose chemotherapy with ASCT.

Proposed Indication

Adult patients with newly diagnosed multiple myeloma who are eligible for high-dose chemotherapy with autologous stem cell transplant (ASCT).[1]

Technology

Description

Daratumumab (Darzalex) is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to the CD38 protein expressed on the surface of cells in a variety of haematological malignancies, including clonal plasma cells in multiple myeloma. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.[2] After binding to CD38, daratumumab inhibits the growth of CD38-expressing tumour cells in several ways, including the induction of apoptosis directly through Fc-mediated cross-linking, induction of immune-mediated tumour-cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis.[3]

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone is currently in clinical development for adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with ASCT. In the phase III clinical trial (PERSEUS; NCT03710603) participants were given 1800mg daratumumab by subcutaneous injection (SC) weekly in cycles 1 and 2, then every 2 weeks in cycles 3-6 (each cycle lasting 28 days). In maintenance cycles (cycles 7+), participants will receive daratumumab once every 4 weeks until disease progression or unacceptable toxicity.[1]

Key Innovation

Mortality amongst multiple myeloma patients remains significant, highlighting the need for new effective treatment options.[4] Daratumumab is specifically designed to target the CD38 protein expressed on the surface of multiple myeloma cells.[5] Studies have demonstrated that the addition of daratumumab to triplet therapy has resulted in improved patient outcomes.[4-6] If licenced, daratumumab with lenalidomide, bortezomib and dexamethasone will offer an additional treatment option for newly diagnosed adult patients with multiple myeloma who are eligible for high-dose chemotherapy with ASCT.

Regulatory & Development Status

Daratumumab has Marketing Authorisation in the EU/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 ASCT.
- In combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for ASCT.
- In combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last 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
- In combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic amyloid light-chain amyloidosis.

Daratumumab in combination with bortezomib, lenalidomide and dexamethasone is currently in clinical development for patients with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy.[7]

Daratumumab monotherapy is in phase II and/or III clinical development a number of other indications, including:[7]

- Neuromyelitis optica
- Waldenstrom macroglobulinemia
- Monoclonal gammopathy
- Plasmablastic lymphoma
- Lymphoma
- Lupus
- POEMS syndrome
- Immune thrombocytopenia
- Membranoproliferative glomerulonephritis
- Transplant rejection
- Chronic lymphocytic leukaemia

Daratumumab was granted an orphan drug designation by the EMA in March 2015 for the treatment of plasma cell myeloma.[8]

Patient Group

Disease Area and Clinical Need

In multiple myeloma, plasma cells inside the bone marrow (the spongy tissue found at the centre of some bones), become cancerous and large numbers of abnormal plasma cells are produced. These cells fill up the bone marrow and interfere with the production of other cells such as red and white blood cells.[9] Multiple myeloma often affects several areas of the body, such as the spine, skull, pelvis and ribs.[10] Multiple myeloma may not cause any symptoms in the early stages but eventually leads to a wide range of symptoms including: bone pain; bone fractures and spinal cord compression; anaemia; repeated infections; hypercalcaemia; unusual bleeding; thickened blood; and kidney problems.[11] The exact cause is unknown, but multiple myeloma is closely associated with monoclonal gammopathy of unknown significance (MUGS). Other factors can also increase risk of developing the disease, with multiple myeloma being most common amongst older people, males, and black populations.[9]

Multiple myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018).[12] The age standardised incidence rate for multiple myeloma in England is 12.4 and 7.6 per 100,000 amongst males and females respectively.[13] In England (2021-22) there were 136,444 finished consultant episodes (FCE) and 131,440 admissions for multiple myeloma (ICD-10 code C90.0) which resulted in 123,961 day cases and 88,511 FCE bed days.[14] In England (2017), there were 5,034 patients diagnosed with multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C90) and 2,611 deaths registered where multiple myeloma and malignant plasma cell neoplasms was the underlying cause.[15] For patients diagnosed with myeloma between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 82.7% and 52.3% respectively.[16]

Recommended Treatment Options

NICE currently recommends the following treatment options for newly diagnosed multiple myeloma when a stem cell transplant is suitable:[17]

- Daratumumab in combination with bortezomib, thalidomide and dexamethasone
- Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide

Clinical Trial Information

Trial	**PERSEUS;** NCT03710603; A phase 3 study comparing daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone (D-VRd) vs VELCADE, lenalidomide, and dexamethasone (VRd) in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy **Phase III** – Active, not recruiting **Locations:** 10 EU countries, Australia, and Turkey **Primary completion date:** May 2025
Trial Design	Randomised, parallel assignment, open-label, active-comparator controlled
Population	N=690; adults aged 18 to 70 years; newly diagnosed multiple myeloma patients for who are eligible for high-dose therapy and autologous stem cell transplantation (ASCT)
Intervention(s)	• Daratumumab (SC, 1800mg) • Lenalidomide (oral administration, 25mg daily in cycles 1-6, then 10mg daily) • Bortezomib (SC, 1.3mg/m2, twice weekly in cycles 1-6) • Dexamethasone (intravenous (IV) administration, 40mg daily on days 1-4 and 9-12 of each cycle)
Comparator(s)	• Lenalidomide (oral, 25mg daily in cycles 1-6, then 10mg daily) • Bortezomib (SC, 1.3mg/m^2, twice weekly in cycles 1-6) • Dexamethasone (IV, 40mg daily on days 1-4 and 9-12 of each cycle)
Outcome(s)	Primary outcome measure: - Progression free survival [Time frame: from randomisation to the date of disease progression or death (approximately up to 9 years)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price for 1 vial of daratumumab (1800mg/15ml) solution for injection is £4,320.[18]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (TA763). February 2022.
- NICE technology appraisal guidance. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy (TA311). April 2013
- NICE clinical guideline. Myeloma: Diagnosis and management (NG35). October 2018

- NICE clinical 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. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

Other Guidance

- British Society of Haematology. Guidelines on the diagnosis, investigation, and initial treatment of myeloma. 2021.[19]
- European Society of Medical Oncology (ESMO). Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2021.[20]

Additional Information

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