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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Daratumumab in addition to pomalidomide and dexamethasone for relapsed or refractory multiple myeloma

NIHRIO ID	20467	**NICE ID**	10104
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	650915

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

SUMMARY

Daratumumab in addition to pomalidomide and dexamethasone is in clinical development for relapsed or refractory multiple myeloma (MM). 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 red and white blood cells and platelets. 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 treatment ('refractory' MM). Most patients will experience serial relapse to existing treatments at some point during their disease course, hence the need for newer treatment combination options.

Daratumumab is a type of immune therapy that acts by inhibiting the growth of cancer cells in MM via a surface protein called CD38. Daratumumab monotherapy is already licenced for relapsed/refractory MM. Pomalidomide in combination with dexamethasone is also currently licenced to treat relapsed/refractory MM. Early findings from trials have demonstrated that the addition of daratumumab to pomalidomide and dexamethasone may further stimulate the immune system and directly act against cancer cells in MM, potentially providing another treatment option for patients whose disease has progressed on previous treatments.

PROPOSED INDICATION

Add-on therapy for patients with relapsed or refractory multiple myeloma (MM) who have received at least 1 prior treatment regimen with both lenalidomide and a proteasome inhibitor and have demonstrated disease progression.[1]

TECHNOLOGY

DESCRIPTION

Daratumumab is an immunoglobin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of 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. 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+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow.[2]

Daratumumab in addition to pomalidomide and dexamethasone is in phase III clinical development for the treatment of patients with relapsed or refractory MM who have received at least 1 prior treatment. In the phase III clinical trial (NCT03180736) daratumumab is given at a dose of 16 mg/kg administered as an intravenous (IV) infusion (Dara IV) or 1800 mg subcutaneously (Dara SC) at weekly intervals for 8 weeks, then every 2 weeks for an additional 16 weeks, then every 4 weeks thereafter. Pomalidomide 4 mg orally is given on days 1 through 21 of each 28-day cycle and dexamethasone 40 mg (20 mg for patients ⩾75 years of age) orally, is given once daily on days 1, 8, 15, and 22 of each 28-day treatment cycle.[1,a]

INNOVATION AND/OR ADVANTAGES

Daratumumab monotherapy works to treat multiple myeloma and in phase III trials, has significantly benefited patients' progression-free survival (PFS) when combined with other standard of care regimens. Additionally pomalidomide and dexamethasone have demonstrated immune modulation, via activation of T cells, which could potentially complement the immunomodulatory effects demonstrated by daratumumab.[3]

Patients with multiple myeloma (MM) typically have recurrent relapses and treatments available have limited efficacy leading to poor survival.[3] Daratumumab in addition to pomalidomide and dexamethasone will provide another option for these patients whose disease have progressed on both lenalidomide and a proteasome inhibitors.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daratumumab is 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 MM who are ineligible for autologous stem cell transplant.
- In combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed MM who are eligible for autologous stem cell transplant.
- As monotherapy for the treatment of adult patients with relapsed/refractory MM, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
- 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 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, headache, hypertension, cough, dyspnoea, diarrhoea, constipation, nausea, vomiting, back pain, muscle spasms, fatigue, peripheral oedema, pyrexia, asthenia and infusion-related reaction.[2]

In July 2013, orphan designation was granted by the European Commission for daratumumab for the treatment of plasma-cell myeloma.[4]

PATIENT GROUP

DISEASE BACKGROUND

Multiple Myeloma (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.[5,6] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[7] Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[8] Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.[9]

The origin of MM is thought to be unknown as malignant cells display various cytogenetic abnormalities.[10] MM is closely associated with a condition called monoclonal gammopathy of unknown significance (MGUS).[6] 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 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.[11] Overall most patients are diagnosed due to symptoms, which can include bone fracture or pain, low red and white blood counts, fatigue, calcium elevation, kidney problems or infections.[6] In many relapse trials, patients often have pronounced symptoms and substantially reduced health-related quality of life (HRQoL). Around 80% of patients experience skeletal destruction, approximately 73% will have anaemia at diagnosis and about 30% of patients present with renal insufficiency.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016 myeloma was the 19th most common cancer in the UK accounting for 2% of all new cancer cases.[13] 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 89 years.[14] Over the last decade, incidence rates have increased by a seventh (15%) represented by an increase in males of 15% and 12% 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.[13] A systematic review and economic evaluation carried in Europe in 2015 found that almost 10% of patients treated were relapsed or refractory to both proteasome inhibitor and immunomodulatory agent based treatment regimes.[15]

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.[16] Almost half (47%) of people diagnosed with myeloma in England and Wales survive their disease for 5 years or more, with a third surviving for 10 years or more (2010-11).[13] In England in 2017, there were 2,611 registrations of death where MM was recorded as the underlying cause.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Most patients experience serial relapse and will be treated with most available agents at some point during their disease course.[17] The choice of therapy in the relapsed setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).[18] 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.[19]

A non-pharmacological treatment option for relapsed or refractory MM is a second autologous stem cell transplant, depending on the response to the first.[20] Patients may also receive medicines and procedures to prevent and treat problems caused by myeloma rather than the condition itself– such as bone pain, fractures and anaemia.[6]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[20]
In instances of first relapse, the guidelines recommend the use of:

- Daratumumab plus bortezomib plus dexamethasone.
- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
- Bortezomib monotherapy – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.

Subsequent relapse treatment may include:

- Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
- Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy.

- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
- Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
- Daratumumab monotherapy for 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.

PLACE OF TECHNOLOGY

If licensed daratumumab in addition to pomalidomide and dexamethasone will offer an additional treatment option for relapsed or refractory multiple myeloma patients who have received at least 1 prior treatment regimen with both lenalidomide and a proteasome inhibitor and have demonstrated disease progression.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT03180736, 2017-001618-27; A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor. **Phase III** **Location(s):** EU countries (not including UK), Serbia and Turkey.
Trial design	Randomized, parallel assignment, open label.
Population	N= 304, relapsed or refractory multiple myeloma, aged ≤18 years.
Intervention(s)	Daratumumab at a dose of 16 mg/kg administered as an IV infusion or 1800 mg subcutaneously at weekly intervals for 8 weeks, then every 2 weeks for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Pomalidomide 4 mg orally on days 1 through 21 of each 28-day cycle and dexamethasone 40 mg (20 mg for patients ⩾75 years of age) orally, once daily on days 1, 8, 15, and 22 of each 28-day treatment cycle.
Comparator(s)	Pomalidomide 4 mg orally on days 1 through 21 of each 28-day cycle and dexamethasone 40 mg (20 mg for patients ⩾75 years of age) orally, once daily on days 1, 8, 15, and 22 of each 28-day treatment cycle.
Outcome(s)	Primary outcome: • Comparison of Progression Free Survival between treatment arms [Time Frame: Assessed monthly from randomization until disease progression (PD) or death whichever occurs first (approximately up to 3 years)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The NHS indicative price for daratumumab is:[21]

- 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)

The NHS indicative price for a pack of 21 x 4 mg pomalidomide (Imnovid) capsules is £8884.00.[22]
The NHS indicative price for a pack of 10 x 40 mg dexamethasone (Neofordex) tablets is £200.00.[23]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1620). Expected date of issue: To be confirmed.
- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). Expected date of issue: January 2021.
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (ID1477). Expected date of issue: August 2020
- NICE technology appraisal. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (TA586). June 2019.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
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- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
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- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[18]
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- 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.[27]

ADDITIONAL INFORMATION

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