Daratumumab monotherapy for relapsed and refractory multiple myeloma

SUMMARY

Daratumumab is intended to be used as a monotherapy for the treatment of relapsed or refractory multiple myeloma following three or more prior lines of treatment. If licensed, daratumumab will offer an additional treatment option for this patient group. Patients who experience relapse after treatment with lenalidomide and bortezomib have a particularly poor prognosis. Daratumumab is a humanised IgG1k monoclonal antibody targeted at CD38, an antigen highly expressed in multiple myeloma cells. Through binding to this antigen, daratumumab mediates the activation of antibody-dependent cellular and complement-dependent cytotoxicity to stimulate the immune system to more effectively kill tumour cells. Daratumumab does not currently have Marketing Authorisation in the EU for any indication.

In 2011, 4,792 people were diagnosed with multiple myeloma in England and Wales, representing a crude incidence of 9 per 100,000 population. In 2009, it was estimated that 39% of patients with multiple myeloma had relapsed disease and 65% of patients with relapsed multiple myeloma had received two or more prior therapies. Myeloma is the 16th most common cause of cancer death in the UK, accounting for 2% of all deaths from cancer. In 2013, there were 2,449 deaths from myeloma in England and Wales; 1,333 (54%) in men and 1,116 (46%) in women.

Treatment options for patients with relapsed or refractory multiple myeloma include hematopoietic cell transplantation, rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Following first relapse, patients are likely to be offered further combination therapy including bortezomib and dexamethasone (+/- cyclophosphamide) or lenalidomide and dexamethasone. Daratumumab is currently in a phase II clinical trial investigating its effect on overall response rate. This trial is expected to complete in October 2016.
TARGET GROUP

- Multiple myeloma: relapsed and refractory – third and subsequent line.

TECHNOLOGY

DESCRIPTION

Daratumumab (NJ 54767414; JNJ-54767414; humanised anti-CD38 monoclonal antibody; HuMax-CD38) is a humanised IgG1K monoclonal antibody targeted at CD38, an antigen highly expressed in multiple myeloma cells and involved in the signalling cascade of two immunological pathways: antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In addition, daratumumab also exhibits effect through antibody-dependent cell-mediated phagocytosis and direct induction of apoptosis. Through binding to CD38 daratumumab mediates these pathways to stimulate the immune system to more effectively kill tumour cells. In one phase II clinical trial, daratumumab was administered by intravenous infusion (IV) at 16mg/kg weekly for 8 weeks, every other week for an additional 16 weeks, and then every 4 weeks thereafter, or administered at 8mg/kg IV every 4 weeks on an ongoing basis.

Daratumumab does not currently have Marketing Authorisation in the EU for any indication. Daratumumab is in phase III clinical trials for relapsed/refractory multiple myeloma as combination therapy and phase II clinical trials for non-Hodgkin’s lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, daratumumab monotherapy will offer an additional treatment option for patients with relapsed and refractory multiple myeloma. Patients who experience relapse after treatment with immunomodulatory agent lenalidomide and proteasome inhibitor bortezomib have a particularly poor prognosis, with median overall survival of nine months.

DEVELOPER

Janssen-Cilag Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Daratumumab is a designated orphan drug in the EU.

Daratumumab is in phase II clinical trials.

PATIENT GROUP

BACKGROUND

Multiple myeloma develops from plasma cells in the bone marrow and is the 17th most common cancer in the UK, accounting for around 1% of all new cases. The uncontrolled over-production of abnormal plasma cells in multiple myeloma results (in the vast majority of patients), in the production of a large amount of a single clone of abnormal antibody and a reduction in the number of normal white blood cells, red cells, and platelets. This leads to...
anaemia, repeated infections, bone lesions, hypercalcaemia, kidney damage, fatigue, and unexplained bruising6.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

In 2011, 4,792 people were diagnosed with multiple myeloma (ICD-10 C90) in England and Wales, representing a crude incidence of 9 per 100,000 population5. Higher incidences, however, are seen in certain ethnic groups3,7, with data for England suggesting that myeloma is almost twice as common in people from Black ethnic groups compared to White ethnic groups5. The risk of developing multiple myeloma increases with age; around 4 out of 10 myeloma cases occur in people aged 75 and over8, with only 15% of patients aged less than 60 years15. In 2013-14, there were 108,369 hospital admissions with a primary diagnosis of multiple myeloma (ICD-10 C90.0) in England, resulting in 91,531 bed days and 112,155 finished consultant episodes9. Myeloma is the 16th most common cause of cancer death in the UK, accounting for 2% of all deaths from cancer. In 2013, there were 2,449 deaths from myeloma in England and Wales; 1,333 (54%) in men and 1,116 (46%) in women10.

Almost half of patients with myeloma in England and Wales now survive their disease for at least 5 years5. The pattern of disease is typically remission followed by relapse requiring further therapy, often 3 or 4 times before the development of treatment resistance. With each relapse, the following remission is usually shorter than the previous one. Relapses become more difficult to treat due to the development of drug resistance and the emergence of bone, renal and haematological problems, which are part of the disease11. Patients whose disease has become refractory to bortezomib and immunomodulatory drugs typically have an overall survival (OS) of 9 months, but only 3 months if they receive no therapy following relapse12. In 2009, it was estimated that 39% of patients with multiple myeloma had relapsed disease and 65% of patients with relapsed multiple myeloma had received two or more prior therapies, which equates to 1,082 people13.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Multiple myeloma (relapsed, refractory) – carfilzomib (after prior therapy) (ID677). Expected date of issue to be confirmed.
• NICE technology appraisal in development. Panobinostat for treating multiple myeloma in people who have received at least one prior therapy (ID663). Expected January 2016.
• NICE technology appraisal in development. Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part-review of TA171) (ID667).
• NICE technology appraisal. Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib (TA338). March 2015.
• 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. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). June 2009.

Other Guidance


CURRENT TREATMENT OPTIONS

Supportive care plays an important role in the management of multiple myeloma as despite modern treatments significantly improving overall and progression free survival, the vast majority of patients remain incurable. Treatment regimens for multiple myeloma are patient specific and dependent on performance status, eligibility for high dose chemotherapy with stem cell transplantation support, and frailty. Induction therapy followed by high-dose melphalan and autologous stem cell transplantation (ASCT) provides the greatest chance of prolonged survival and complete remission; however this typically only improves survival by up to a year. This treatment is also limited to patients who are able to tolerate it; in Europe, ASCT is primarily offered to patients less than 65 years of age, and is usually only considered in the absence of any serious heart, lung, renal and liver dysfunction. As the median age at diagnosis is 65 years, approximately 30-40% of newly diagnosed multiple myeloma patients are likely to be ineligible for this therapy. The aim in such patients is to give effective combination therapy, which may include melphalan, prednisolone, and thalidomide; cyclophosphamide, dexamethasone, and thalidomide; or bortezomib, melphalan, and prednisolone.

Treatment options for patients with relapsed or refractory multiple myeloma include hematopoietic cell transplantation, rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Expert opinion suggests that following first relapse, patients are likely to be offered further combination therapy including:

• Bortezomib and dexamethasone +/- cyclophosphamide.
• Lenalidomide and dexamethasone (licensed for use following first relapse, but only approved by NICE for patients who have received 2 or more prior therapies).

Lenalidomide in combination with dexamethasone is a treatment option for patients with multiple myeloma who have received two or more prior therapies. In patients with relapsed or refractory multiple myeloma, lenalidomide can overcome resistance to conventional chemotherapy and dexamethasone plus lenalidomide is more effective than either agent.
alone in refractory multiple myeloma. Expert opinion suggests that lenalidomide and dexamethasone is widely used alongside first line treatment with bortezomib through the Cancer Drugs Fund.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01985126, CR102651, 54767414MMY2002, 2013-000752-18; daratumumab; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Janssen Research and Development.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
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<tr>
<td>Location</td>
<td>Canada, Spain and USA.</td>
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<tr>
<td>Design</td>
<td>Randomised.</td>
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<tr>
<td>Participants</td>
<td>n=124; aged ≥ 18 years; multiple myeloma with disease progression on most recent treatment regimen, at least 3 prior lines of therapy with disease double refractory to both proteasome inhibitor therapy and immunomodulatory drugs.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to daratumumab at 16mg/kg IV weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter; or 8mg/kg every 4 weeks; both in combination with prophylactic IV methylprednisolone, acetaminophen 650-1,000mg oral, and diphenhydramine 25-50mg oral, all administered prior to and after study drug administration.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment until disease progression.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Overall response rate (ORR).</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Number of participants with adverse events, duration of and time to response, clinical benefit rate, progression free survival (PFS), time to disease progression, pharmacokinetics, anti-drug antibodies, soluble CD38 levels, complement inhibitory protein expression, antibody-dependent cell-mediated cytotoxicity expression, complement-dependent cytotoxicity expression.</td>
</tr>
<tr>
<td>Key results</td>
<td>ORR was 29% in patients receiving 16mg/kg of daratumumab. Median PFS was 3.7 months. Median overall survival could not yet be calculated, 1-year overall survival is 65%.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>Serious treatment-emergent adverse effects (TEAEs) occurred in 30% of patients, 23% had grade 3-4 TEAEs. No discontinuations of treatment were due to daratumumab-related AE.</td>
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</table>

### ESTIMATED COST and IMPACT

#### COST

The cost of daratumumab in the UK is not yet known. The costs of other selected treatments for multiple myeloma are summarised in the following table.

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**Drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost per cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (Velcade)</td>
<td>3.5mg IV for nine 6-week cycles. Days 1, 4, 8, 11, 22, 25, 29 and 32 in cycles 1 to 4 and days 1, 8, 22 and 29 in cycles 5 to 9. Expert opinion suggests a maximum of 32 doses is administered.</td>
<td>3.5mg vial cost £762.38</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td>25mg orally on days 1 to 21 of a 28 day cycle</td>
<td>£4,368 per treatment cycle</td>
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<tr>
<td>Pomalidomide (Imnovid)</td>
<td>4mg orally on days 1 to 21 of a 28 day cycle</td>
<td>£8,884 per treatment cycle</td>
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**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability: *the company suggests daratumumab is expected to increase PFS with an associated reduction in symptom burden*.  
- Other
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services: *service impact due to eight hour IV infusion taking significant day case time with possible admission required*.  
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: *uncertain unit cost compared to existing treatments.*  
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified.
- No impact identified

**REFERENCES**

1. ClinicalTrials.gov. An efficacy and safety study of daratumumab in patients with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or are double refractory to a PI and an IMiD.  

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*a Company comments*
15 British Committee for Standards in Haematology (BCSH) in conjunction with the UK myeloma forum. Guidelines for the diagnosis and management of multiple myeloma. London: BCSH; August 2013.
19 NIHR Horizon Scanning Research and Intelligence Centre. Panobinostat (Faridak) for relapsed or refractory multiple myeloma. University of Birmingham, April 2012. http://www.hsc.nihr.ac.uk/
20 National Institute for Health and Clinical Excellence. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). London: NICE; June 2009.
23 ClinicalTrials.gov. An efficacy and safety study of daratumumab in patients with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or are double refractory to a PI and an IMiD. https://www.clinicaltrials.gov/ct2/show/record/NCT01985126 Accessed 15 June 2015.