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Daratumumab in combination with bortezomib, melphalan and prednisone for multiple myeloma – first line

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LAY SUMMARY

Multiple myeloma (MM) is a rare, incurable cancer of the plasma cells in the bone marrow. Bone marrow is the spongy tissue found at the centre of some bones, which produces blood cells for the body. Plasma cells are normally produced in a controlled way but in cases of MM, large amounts of abnormal plasma cells are produced. These fill the bone marrow and interfere with the production of other cells, including red and white blood cells and platelets. The cause of MM is unknown. Symptoms of MM varies but some may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections.

Daratumumab in combination with bortezomib, melphalan and prednisone is in development for multiple myeloma in patients who are newly diagnosed and ineligible for stem cell transplant and high dose chemotherapy. The combination of bortezomib, melphalan and prednisone is already licensed in the UK to treat MM in patients who are newly diagnosed and ineligible for stem cell transplant and high dose chemotherapy. The addition of daratumumab has been shown to lower the risk of disease progression or death. If licensed, this new combination, may offer an additional first line treatment option for this MM patient group who have few treatment options.

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TARGET GROUP

Multiple myeloma (MM) (ineligible for stem cell transplant and high dose chemotherapy, newly diagnosed or previously untreated) – first line add-on therapy; in combination with bortezomib, melphalan and prednisone

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 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]

Bortezomib (Velcade) is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.[2]

Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-2-chlorethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands and thereby preventing cell replication.[3]

Prednisone is a non-fluorinated glucocorticoid for systemic therapy. Prednisone has an immediate anti-inflammatory (antiexsudative and antiproliferative) effect and a delayed immunosuppressive effect. It inhibits chemotaxis and the activity of immune cells as well as the release and effect of mediators of inflammatory and immune reactions, e.g. of lysosomal enzymes, prostaglandins and leukotrienes.[4]

Daratumumab in combination with bortezomib, melphalan and prednisone is in development as a first line treatment option for patients with newly diagnosed, MM who are ineligible for stem cell transplant and high dose chemotherapy. In the phase III clinical trial (NCT02195479), participants will receive bortezomib at a dose of 1.3 milligram per square meter (mg/m^2) as subcutaneous injection, twice weekly at weeks 1, 2, 4 and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4 and 5 in cycles 2 to 9. Melphalan will be administered at a dose of 9 mg/m^2, orally, once daily (on days 1-4) and prednisone will be given at a dose of 60 mg/m^2 orally once daily, on days 1 to 4 of each cycle up to cycle 9. In addition to this, participants will also receive daratumumab at a dose of 16 mg/kg as an intravenous infusion, once weekly, for 6 weeks in cycle 1 and then every 3 weeks, in cycle 2 to 9 and thereafter, once every 4 weeks until documented progression, unacceptable toxicity, or study end. On days when daratumumab is given, intravenous or oral dexamethasone at a dose of 20 mg, is given 1 hour or less prior to daratumumab infusion as pre-medication and prednisone substitute, and oral prednisone at a dose of 60 mg/m2 once daily will be given on days 2-4.[5]

The most frequent adverse events (> 20%) in MM patients treated with daratumumab were infusion reactions, fatigue, nausea, diarrhoea, muscle spasms, pyrexia, cough, dyspnoea, neutropenia,

thrombocytopenia and upper respiratory tract infection. In addition, in combination with bortezomib, peripheral oedema and peripheral sensory neuropathy were frequently reported. Also, pneumonia was among the very common adverse reactions (≥ 1/10) whereas influenza and atrial fibrillation were among the common adverse reactions (≥ 1/100 to < 1/10).[1]

The most commonly reported adverse events during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.[2]

The most common adverse events associated with melphalan vary largely across the indication that is being treated.[3]

Daratumumab in combination with bortezomib, melphalan and prednisone does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licenced, daratumumab in combination with bortezomib, melphalan and prednisone for MM has the potential to become the first antibody based regime for the treatment of newly diagnosed multiple myeloma that is not eligible for stem cell transplant.[6] Clinical research indicates that the addition of daratumumab to this treatment combination can lower the risk of disease progression or death when compared to the same treatment combination without daratumumab.[7]

If licensed, daratumumab in combination with bortezomib, melphalan and prednisone may offer a first line treatment option for patients with newly diagnosed, multiple myeloma who are ineligible for stem cell transplant and high dose chemotherapy.

DEVELOPER

Janssen-Cilag Ltd

PATIENT GROUP

BACKGROUND

MM is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin in the serum or urine.[8] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[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). In almost all cases, MM occurs in those who have previously had MGUS.[11] MGUS is characterised by an excess number of protein molecules (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. 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.[12]

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.[9] Other features and symptoms of MM can 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] Most commonly patients display increased infection susceptibility or bone pain, or both. Hypercalcaemia can be a result of the release of calcium from the bone to the blood stream, and the high protein concentration in serum can lead to renal failure. MM can manifest into end-organ damage, which has major implications on patient quality of life. This represents an important point in the treatment pathway of MM as it indicates the requirement to begin aggressive treatment.[14] Following aggressive treatment, it is indicated that outcomes may only be improved by autologous stem cell transplantation.[15] However, following the consideration of biological age, Eastern Cooperative Oncology Group performance status, the comorbidities experienced and level of renal failure, some patients are ineligible for this treatment.[10]

CLINICAL NEED and BURDEN OF DISEASE

In 2015, MM was the 19th most common cancer in the UK with 4,920 new cases in England and Wales (2,835 male and 2,085 female). MM incidence is strongly linked to age, with almost half (45%) of new cases diagnosed in the UK between 2013-2015 presenting in persons aged 75 years and older. MM incidence rates are projected to rise by 11% in the UK between 2014 and 2035, from 13.76 per 100,000 to 15.52 per 100,000. It is anticipated that around 90% of all newly diagnosed MM patients in the UK receives an active treatment and of those, 75% are likely to be ineligible for an autologous stem cell transplant. Applying these proportions to the incidence figure for 2015 means that 3,284 newly diagnosed MM patient would have been eligible for treatment under this indication that year.[a]

In 2016-17 NHS England reported 140,645 finished consultant episodes (FCEs) and 136,025 admissions under ICD code C90.0 (multiple myeloma) resulting in 90,685 FCE bed days.[16] There were 3,079 MM deaths in 2016, accounting for 2% of all cancer mortality in the UK.[17]

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).[18] Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, immunomodulatory drugs and proteasome inhibitors, and the adoption of haematopoietic stem cell transplantation.[19]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Elotuzumab for multiple myeloma (ID966). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Multiple myeloma (newly diagnosed) - lenalidomide (ID474). Expected June 2018.
- NICE technology appraisal guidance. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.

[a] Company submission regarding TA437

- NICE technology appraisal guidance. Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (TA228). July 2011.
- NICE technology appraisal guidance. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.

NHS ENGLAND and POLICY 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[19]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017[20]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015[21]
- 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[22]
- The European Myeloma Network. European Myeloma Network Guidelines: European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. 2014[23]
- International Myeloma Working Group. Guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation. 2009[24]

CURRENT TREATMENT OPTIONS

Despite recent progress, MM remains incurable and the majority of patients will progress and require treatment. The health 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. Patients with MM typically undergo courses of treatment. 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.[19]

There is currently no cure for MM, but treatment can often help control it for several years. Treatment often involves anti-myeloma medications to destroy the myeloma cells, medicines and procedures to prevent and treat problems caused by myeloma, such as bone pain, fractures and anaemia.[25]

NICE guideline (NG35) for management of newly diagnosed myeloma recommends the following treatments:[26]

- Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.
- Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
    - High-dose chemotherapy with stem cell transplantation is considered inappropriate and
    - The person is unable to tolerate or has contraindications to thalidomide.

EFFICACY and SAFETY

Trial	NCT02195479, EudraCT 2014-002272-88; daratumumab in combination with bortezomib, melphalan and prednisone vs bortezomib, melphalan and prednisone combination therapy; phase III
Sponsor	Janssen-Cilag Ltd
Status	Published
Source of Information	Trial registry,[5] and publication[7]
Location	EU (incl UK), USA and other countries
Design	Randomised, active-controlled, parallel assignment, open-label study
Participants	n=706; aged ≥18 years; multiple myeloma in patients who are newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation (SCT) due to: being age >=65 years, or in participants <65 years: presence of important comorbid conditions likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation.
Schedule[b]	Participants were randomised to: Receive up to nine cycles (42-day cycles) of bortezomib at a dose of 1.3 mg/m^2 subcutaneously, twice weekly at weeks 1, 2, 4 and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4 and 5 in cycles 2 to 9. Oral melphalan will be administered at a dose of 9 mg/m^2, once daily (on days 1-4) and oral prednisone will be given at a dose of 60 mg/m^2, once daily, on days 1 to 4 of each cycle up to cycle 9. In addition to this, participants will also receive daratumumab at a dose of 16 mg/kg of body weight as an intravenous infusion, once weekly, for 6 weeks in cycle 1 and then every 3 weeks, in cycle 2 to 9 (cycles 1-9: 6-week cycles). Post-administration of bortezomib, melphalan and prednisone (beyond cycle 9), daratumumab is given once every 4 weeks until documented progression, unacceptable toxicity, or study end. On days when daratumumab is given, intravenous or oral dexamethasone at a dose of 20 mg, is given 1 hour or less prior to daratumumab infusion as pre medication and prednisone substitute, and oral prednisone at a dose of 60 mg/m^2 once daily will be given on days 2-4.

[b] Company information

	OR Receive up to nine cycles (42-day cycles) of bortezomib 1.3 mg/m^2 subcutaneously, twice weekly at weeks 1, 2, 4 and 5 in cycle 1 followed by once weekly at weeks 1, 2, 4 and 5 in cycles 2 to 9. Oral melphalan will be administered at a dose of 9 mg/m^2, once daily (on days 1-4) and oral prednisone 60 mg/m^2, once daily, on days 1 to 4 of each cycle up to cycle 9.
Follow-up	Median follow up: 16.5 months.
Primary Outcomes	Progression-free survival [Time Frame: Assess at approximately 41 months from randomisation]
Secondary Outcomes	Time to Disease Progression [Time Frame: Assess at approximately 41 months from randomisation] Complete Response [Time Frame: Assess at approximately 41 months from randomisation] Minimal Residual Disease Negativity Rate [Time Frame: Assess at approximately 41 months from randomization] Progression Free Survival on Next Line of Therapy [Time Frame: Assess at approximately 41 months from randomisation] Time to Next Treatment [Time Frame: Assess at approximately 41 months from randomisation] Overall Response Rate [Time Frame: Assess at approximately 41 months from randomisation] Stringent Complete Response [Time Frame: Assess at approximately 41 months from randomisation] Very Good Partial Response or Better [Time Frame: Assess at approximately 41 months from randomisation] Time to Response [Time Frame: Assess at approximately 41 months from randomisation] Duration of Response [Time Frame: Assess at approximately 41 months from randomisation] Overall Survival [Time Frame: Assess at approximately 41 months after first participant randomised up to a maximum of 5 years after last participant is dosed] Impact of daratumumab in combination with bortezomib, melphalan and prednisone compared to bortezomib, melphalan and prednisone combination therapy on patient-reported perception of global health. [Time Frame: Assess at approximately 41 months from randomization]

	Clinical efficacy of daratumumab in combination with bortezomib, melphalan and prednisone in high risk molecular subgroups compared to bortezomib, melphalan and prednisone combination therapy alone. [Time Frame: Assess at approximately 41 months from randomisation]
Key Results	The 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumour cell per 10^5 white cells), as compared with 6.2% of those in the control group (P<0.001). Among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab.
Adverse effects (AEs)	The most common adverse events of grade 3 or 4 were haematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anaemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Daratumumab is marketed in the UK; a 100mg/5ml vial (20mg/mL) costs £360.00.[27]

Bortezomib is marketed in the UK; a vial (3.5 mg power for solution for injection) costs £762.38.[28]

Melphalan is marketed in the UK; a pack of 25 x 2mg tablets costs £45.38.[29]

Prednisone is marketed in the UK; a pack of 30 x 5mg modified-release tablets costs £26.70.[30]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ 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: *reduced use of secondary care/specialist services*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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