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Daratumumab (Darzalex) with lenalidomide and dexamethasone for multiple myeloma – first line

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LAY SUMMARY

The bone marrow is the spongy tissue found at the centre of some bones. It produces the body's blood cells. Multiple myeloma is a type of bone marrow cancer that affects the production of plasma cells (a type of blood cell) inside the bone marrow. Myeloma does not usually take the form of a lump or tumour. Instead, the myeloma cells divide and expand within the bone marrow, damaging the bones and affecting the production of healthy blood cells. Myeloma often affects many places in the body, which is why it is called multiple myeloma. Commonly affected areas include the spine, skull, pelvis and ribs.

Daratumumab is a new drug for the treatment of multiple myeloma (Kahler disease). The drug acts by targeting some specific cells that destroys the cancer cells and also improve the body's natural immune response. The safety and efficacy of daratumumab is currently being evaluated for use in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma (a blood cancer of plasma cells) who are not candidates for high dose chemotherapy and autologous stem cell transplant.

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TARGET GROUP

Multiple myeloma – first line; in combination with lenalidomide and dexamethasone

TECHNOLOGY

DESCRIPTION

Daratumumab (Darzalex) is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line. It is formulated as solution for intravenous route of administration. Daratumumab monotherapy is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) and who have demonstrated disease progression on the last therapy. Daratumumab is also indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.[1]

The mechanisms of action of daratumumab comprise immune-mediated effects, including complement-dependent and antibody-dependent cell-mediated cytotoxic effects, antibody-dependent cellular phagocytosis, and apoptosis by means of cross-linking.[2,3] Moreover, daratumumab may have a role in immunomodulation by means of depletion of CD38-positive regulator immune suppressor cells, which leads to a greater clonal expansion of T cells in patients who have a response than in those who do not.[4]

A phase III clinical trial is being planned to assess the efficacy, safety, pharmacokinetics and pharmacodynamics of daratumumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in treating subjects with newly diagnosed multiple myeloma. In this trial the experimental arm, daratumumab is administered by intravenous (IV) infusion at 16 milligram per kilogram (mg/kg), once a week for 8 weeks, then once every other week for 16 weeks, thereafter once every 4 weeks until documented progression of disease, unacceptable toxicity or end of study (maximum up to 7 years). Lenalidomide 25 mg capsule orally on day 1 through day 21 of each 28-day cycle, until disease progression or unacceptable toxicity, and dexamethasone 40 mg orally or intravenously once a week until disease progression or unacceptable toxicity, whichever comes first.[5]

Daratumumab is licensed in the EU and UK as a therapeutic agent for refractory multiple myeloma and relapsed multiple myeloma and has been designated orphan drug for these two indications. Daratumumab is also under global development for the treatment of:[6]

- Amyloidosis (phase II)
- Prostate Cancer; Non-Small Cell Lung Cancer; Myelodysplastic Syndrome; Natural Killer Cell Lymphomas; T-Cell Lymphomas (phase II)
- Waldenstrom Macroglobulinemia; Acute Lymphocytic Leukemia (ALL, Acute Lymphoblastic Leukemia); Refractory Acute Myeloid Leukemia; Relapsed Acute Myeloid Leukemia (phase I)
- Chronic Lymphocytic Leukemia (CLL) (Preclinical)

INNOVATION and/or ADVANTAGES

If approved, daratumumab in combination with lenalidomide and dexamethasone will offer an additional treatment option for patients with previously untreated multiple myeloma. Daratumumab in combination with lenalidomide and dexamethasone has the potential to prolong progression-free survival (PFS) as compared with lenalidomide and dexamethasone alone in subjects with newly

diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant. The PFS is defined as time from date of randomization to either progressive disease (PD), or death, whichever occurs first. PD will be determined according to International Myeloma Working Group (IMWG) criteria.[6]

DEVELOPER

Janssen-Cilag Ltd

AVAILABILITY, LAUNCH or MARKETING

The company anticipate submitting a Marketing Authorisation Application to EMA in Q1 2019.

PATIENT GROUP

BACKGROUND

Myeloma (also known as multiple myeloma) is a cancer in which there is abnormal growth in the number of plasma cells in the bone-marrow and blood. This can suppress the normal production of blood cells, including those associated with the body's immune system. The plasma cells may collect in the bone to make small tumours known as plasmacytomas. Myeloma is most common in people aged over 60, and is rare before the age of 40.[7]

Survival of patients with multiple myeloma has been extended markedly in the last 15 years and patients living with the disease for 10–15 years are no longer rare.[8]

The cause of multiple myeloma has not been determined. However, a number of possible associations have been identified: [9]

- Decreased immune system function; the immune systems of older individuals may be less efficient at detecting and destroying cancer cells
- Genetic (hereditary) factors, suggested by the increased incidence in some ethnic groups and among family members
- Occupational factors, suggested by the increased incidence among agricultural, petroleum, wood, leather workers and cosmetologists
- Long-term exposure to herbicides, pesticides, petroleum products, heavy metals, plastics and dusts such as asbestos
- Radiation exposure, as among Japanese atomic bomb survivors, nuclear weapons workers and medical personnel such as radiologists
- Kaposi's sarcoma-associated herpes virus (also called human herpes virus-8 or HHV-8), found in the blood and bone marrow cells of many multiple myeloma patients

In the early stages, multiple myeloma may not cause any symptoms or complications, and may only be diagnosed after a routine blood or urine test. However, it will eventually cause a wide range of problems including: [10]

- Bone pain
- Bone fractures and spinal cord compression
- Anaemia
- Repeated infections

- Raised calcium levels in the blood
- Unusual bleeding
- Kidney problem

Patients with multiple myeloma experience a much lower quality of life (QoL) compared with the general population, irrespective of the number of years since diagnosis.[11] Studies in patients with relapsed or refractory multiple myeloma have demonstrated clinically relevant improvements in certain QoL and symptom scores with novel treatments, and in transplant setting studies response and improved long-term outcomes are associated with an overall improvement in QoL.[12,13]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 5,501 new cases of myeloma in the UK. 3,072 (56%) in men and 2,429 (44%) in women, giving a male: female ratio of around 13:10. The crude incidence rate shows that there are 10 new myeloma cases for every 100,000 males in the UK and 7 for every 100,000 females. Almost half (45%) myeloma cases in the UK each year are diagnosed in people aged 75 and over (2012-2014).[14]

In that same year, approximately 2,928 people died of this condition. Almost 33% of people diagnosed with multiple myeloma cancer in England and Wales survive for ten years or more (2010-11).[14]

In 2015/2016 Hospital Episodes Statistics for multiple myeloma and malignant plasma cell neoplasms amounted for 133,492 finished consultant episodes (FCE), 129,217 admissions and 87,528 FCE bed days (ICD-10 codes C90). [15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Multiple myeloma (newly diagnosed) – lenalidomide [ID474]. Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). July 2011.
- NICE technology appraisal guidance. Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation (TA311). April 2014.
- 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. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Patients, Multiple Myeloma. 2016.[16]

- European Society for Medical Oncology. Multiple Myeloma: ESMO clinical practice guidelines. 2017. [17]

CURRENT TREATMENT OPTIONS

There is currently no cure for multiple myeloma, but treatment can often help control it for several years. Treatment will often involve a combination of 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 and anti-myeloma medicines to control the cancer when it comes back (relapses).[10]

NICE guideline (NG35) for management of newly diagnosed myeloma recommends the following treatments: [18]

- 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	NCT02252172; phase III trial
Sponsor	Janssen-Cilag Ltd
Status	Ongoing, not recruiting
Source of Information	Trial registry [5]
Location	7 of EU countries (incl UK)
Design	Randomised, active-controlled, open-label trial
Participants	N= 730 planned; 18 years and older; newly diagnosed multiple myeloma
Schedule	Randomised to: Experimental: Daratumumab 16mg/kg IV infusion weekly for first 8 weeks, every other week for 16 weeks and then every 4 weeks in combination with lenalidomide 25 mg capsule orally on day 1 through day 21 of each 28-day cycle and dexamethasone 40 mg orally or intravenously once a week until disease progression or unacceptable toxicity, whichever comes first

	Active comparator: Lenalidomide 25 mg capsule orally on day 1 through day 21 of each 28-day cycle and dexamethasone 40 mg orally or intravenously once a week until disease progression or unacceptable toxicity.
Follow-up	5 years
Primary Outcomes	Progression-Free Survival (PFS) Time
Secondary Outcomes	Time to Disease Progression (TTP) Percentage of Participants With Complete response (CR) Minimal Residual Disease (MRD) Negativity Rate Progression-Free Survival on Next Line of Therapy (PFS2) Overall Survival (OS) Time Percentage of Participants With Stringent Complete Response (sCR) Time To Next Treatment Percentage of Participants With Overall Response (OR) Percentage of Participants With Very Good Partial Response (VGPR) or Better Response Time to Response Duration of Response (DR) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score Euro Quality of Life (EQ-5D-5L) Health State Profile Utility Score
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of daratumumab for previously untreated multiple myeloma estimated to be £3.60 per mg (dose is 16 mg/Kg), cost will vary with patient weight and treatment duration.[19]

Daratumumab is already marketed in the UK for the treatment of relapsed and refractory multiple myeloma; a 100mg/5ml vial costs £360 and 400mg/20ml vial costs £1440.[20]

Drug	Dose[21]	Unit cost[21]
Bortezomib (Janssen-Cilag Ltd) – Powder for solution for injection vials	Nine 6-week treatment cycles: In cycles 1–4: twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In cycles 5–9: once weekly (days 1, 8, 22 and 29).	£762.38/3.5mg
Thalidomide (Celgene Ltd) – capsules	For Adult 18–75 years: 200 mg once daily for 6–week cycle for a maximum of 12 cycles For Adult 76 years and over: 100 mg once daily for 6–week cycle for a maximum of 12 cycles.	£10.66/50mg
Lenalidomide (Celgene Ltd) – capsules	For Adult: 25 mg once daily for 21 consecutive days of repeated 28-day cycles in combination with dexamethasone 10 mg once daily for 21 consecutive days of repeated 28-day cycles for up to 9 cycles in combination with melphalan and prednisone	 £208/25mg £180/10mg

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: *improved quality of life for carers, improved patient convenience*

☐ 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

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☐ None identified

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