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Lenalidomide (Revlimid) for newly diagnosed 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 (MM) is a type of bone marrow cancer that affects the production of plasma cells (a type of blood cell) inside the bone marrow. MM does not usually take the form of a lump or tumour. Instead, the plasma cells divide and expand within the bone marrow, damaging the bones and affecting the production of healthy blood cells. MM often affects different parts of the body, which is why it is called multiple myeloma. Commonly affected areas include the spine, skull, pelvis and ribs.

Lenalidomide in combination with bortezomib and dexamethasone is being developed for the treatment of adult patients with MM. While each of these drugs are already approved for treating a range of malignant blood diseases, the combination of the three drugs has shown significant potential particularly for the treatment of newly diagnosed MM. If approved, it will offer an additional treatment option for adult patients whether or not they are eligible or ineligible for bone marrow transplant.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Multiple myeloma; first line treatment for newly diagnosed adult patients with previously untreated multiple myeloma either eligible or ineligible for transplant

TECHNOLOGY

DESCRIPTION

The technology under development is a combination therapy of lenalidominde with bortezomib and dexamethasone.

Lenalidomide is an oral, immunomodulatory drug derived from thalidomide.[1] Lenalidomide has anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, it acts by inhibiting the proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells). Lenalidomide acts intracellularly by binding to cereblon, a component of a ubiquitin ligase enzyme complex. In the presence of lenalidomide, cereblon binds to the lymphoid transcriptional factors Aiolos and Ikaros, which leads to their ubiquitination and subsequent degradation, thus resulting in cytotoxic and immunomodulatory effects.[2]

Bortezomib works by blocking or slowing down the action of proteasomes. When proteasome activity is blocked or slowed down, proteins in the cells accumulate causing cells, especially cancerous cells, to stop growing, dividing, and multiplying, leading to cell death.[3]

Dexamethasone is an anti-inflammatory corticosteroid that has been shown to induce multiple myeloma cell death (apoptosis). Dexamethasone apoptotic activity is enhanced by the combination with thalidomide or its analogues and with proteasome inhibitor (e.g. bortezomib).[4]

In the trial NCT00644228, patients were given 25 mg oral lenalidomide once a day on days 1–14 plus 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 and bortezomib was given at 1-3 mg/m^2 intravenously on days 1, 4, 8, and 11.[5]

The combination of lenalidomide, dexamethasone and bortezomib does not currently have a licence or marketing authorisation in the EU for any indication.

The European Commission granted a marketing authorisation valid throughout the European Union for lenalidomide in June 2007. [6] Lenalidomide is licensed in the EU for multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma.[7]

Lenalidomide is currently in phase III trials for:[8]

- Follicular Lymphoma
- B-Cell Chronic Lymphocytic Leukaemia
- Non-Hodgkin Lymphoma
- Myelodysplastic Syndrome
- Diffuse Large B-Cell Lymphoma
- B-Cell Non-Hodgkin Lymphoma
- Extranodal Marginal Zone B-Cell Lymphoma (Mucosa-Associated Lymphoid Tissue or MALT-Lymphoma)
- Mantle Cell Lymphoma

Bortezomib has a UK marketing authorisation for use in combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation.[9]

Bortezomib is also indicated in combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.[10,11]

INNOVATION and/or ADVANTAGES

Multiple myeloma (MM) still remains a rare, incurable, malignant haematological disease. The combination of bortezomib with lenalidomide and dexamethasone has shown significant efficacy in the setting of newly diagnosed MM. If approved, it will offer an additional treatment option for patients with both transplant ineligible and transplant eligible newly diagnosed multiple myeloma.

DEVELOPER

Celgene Ltd

AVAILABILITY, LAUNCH or MARKETING

Lenalidomide is a designated orphan drug in the EU/USA for mantle cell lymphoma, multiple myeloma, follicular lymphoma and acute lymphocytic leukaemia.[12]

PATIENT GROUP

BACKGROUND

The bone marrow is the spongy tissue found at the centre of some bones. It produces the body's blood cells. Multiple myeloma (MM) affects the plasma cells (a type of blood cell) inside the bone marrow. Myeloma cells divide and expand within the bone marrow, damaging the bones and affecting the production of healthy blood cells. Myeloma often affects different parts in the body, which is why it is called multiple myeloma. Commonly affected areas include the spine, skull, pelvis and ribs.[13]

The presentation of MM can range from being asymptomatic to severely symptomatic, with complications requiring emergent treatment. Systemic ailments include bleeding, infection, and renal failure; pathologic fractures and spinal cord compression may occur. Presenting symptoms of MM include bone pain, pathologic fractures, weakness, malaise, bleeding, anaemia, infection (often pneumococcal), hypercalcemia, spinal cord compression, renal failure and neuropathies.[14]

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

The introduction of new drugs in the treatment of patients eligible for autologous stem cell transplantation (ASCT) has allowed for a significant increase of complete response rate with a positive impact on progression-free survival. Induction therapy followed by high-dose melphalan and ASCT provides the greatest chance of prolonged survival and complete remission. However, this treatment

is limited to patients who are able to tolerate it; in Europe ASCT is primarily offered to patients under 65 years of age.[16]

CLINICAL NEED and BURDEN OF DISEASE

MM was the 18th most common cancer in the UK in 2014 and accounted for 5,500 new cases (2% of all new cancer cases). Incidence rates for myeloma are projected to rise by 11% in the UK between 2014 and 2035, to 12 cases per 100,000 people by 2035.[17]

A third (33%) of people diagnosed with myeloma in England and Wales survive their disease for ten years or more (2010-11). Almost half (47%) of people diagnosed with myeloma in England and Wales survive their disease for five years or more (2010-11). More than three-quarters (77%) of people diagnosed with myeloma in England and Wales survive their disease for one year or more (2010-11).[17]

The Hospital Episodes Statistics for England 2015/2016 recorded 133,492 finished consultant episodes (FCE), 129,217 hospital admissions and 87528 FCE beds due to multiple myeloma and malignant plasma cell neoplasms (ICD-10 code C90.0).[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Daratumumab for multiple myeloma (ID933). Expected publication date: To be confirmed
- NICE technology appraisal guidance in development. Elotuzumab for multiple myeloma. (ID966). Expected date of publication: 24th January, 2018.
- NICE technology appraisal guidance in development. Multiple myeloma (newly diagnosed) - lenalidomide (GID-TAG429). Expected publication date: 20th 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.
- NICE technology appraisal guidance. Bortezomib and thalidomide for the first-line treatment of multiple myeloma (TA228). July 2011
- NICE clinical guideline. Myeloma: diagnosis and management. (NG35). February 2016.
- NICE diagnostic guidance in development. Multiple myeloma and related disorders – Freelite assays (and alternative technologies identified during scoping for diagnosis in primary care (GID-DT28). Expected publication date: TBC.

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: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

Moreau P, Miguel JS, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, Hajek R, Dimopoulos MA, Ludwig H, Einsele H, Zweegman S, Facon T, Cavo M, Terpos E, Goldschmidt H, Attal M and Buske C. Multiple myeloma: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2017; 28(4): 52-61.[19]

National Comprehensive Cancer Network. *NCCN Guidelines Version 3. 2017*. NCCN Evidence Blocks: Myeloma Therapy.[20]

Engelhardt M, Terpos E, Kleber M et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. European Myeloma Network Guidelines. *Haematologica* 2014;99:232–42.[21]

CURRENT TREATMENT OPTIONS

There is currently no cure for multiple myeloma, 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.[22]

NICE guideline (NG35) for management of newly diagnosed myeloma recommends the following treatments:[23]

- 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:

    - o High-dose chemotherapy with stem cell transplantation is considered inappropriate and
    - o The person is unable to tolerate or has contraindications to thalidomide.

EFFICACY and SAFETY

Trial	SWOG-S0777; NCT00644228, NCI-2009-00798; newly diagnosed, previously untreated, adults, in combination dexamethasone and bortezomib, phase III.
Sponsor	National Cancer Institute
Status	Ongoing
Source of Information	Trial registry,[5] Publication[24]
Location	USA, Puerto Rico and Saudi Arabia

Design	Randomised, open-label
Participants	n=525 (enrolled); aged 18years or older; adults; multiple myeloma, newly diagnosed, previously untreated, patients without immediate intent for autologous stem cell transplant.
Schedule	ARM A: Lenalidomide, bortezomib and dexamethasone (Induction Schedule) Bortezomib was given at 1.3mg / m^2 intravenously on days 1, 4, 8, and 11 combined with 25 mg oral lenalidomide once a day on days 1–14 plus oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. This combination was given for eight 21 day cycles. ARM B: Lenalidomide & dexamethasone (Induction Schedule) Lenalidomide was given at 25mg orally once a day on days 1–21 with 40 mg oral dexamethasone on days 1, 8, 15, and 22. This combination was given for six 28 day cycles. Upon completion of induction, all patients received ongoing maintenance with 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle. Stem-cell collection was allowed for those patients considering future transplant.
Follow-up	After completion of study treatment, patients are followed up periodically for up to 6 years.
Primary Outcomes	Progression-free survival
Secondary Outcomes	• Overall Survival • Response Rates • Safety
Key Results	The study met its primary objective and showed significant improvement in progression-free survival in the group given lenalidomide, dexamethasone and bortezomib (HR:0.712, one sided *p* value *p*=0.0018, two sided *p* value *p*=0.0037). with an unstratified median progression free survival of 43 months (95% CI 39–52) for lenalidomide, dexamethasone and bortezomib versus 30 months (25–39) for the lenalidomide and dexamethasone group.[24] Response duration was assessed and suggested improved response duration in patients receiving lenalidomide, dexamethasone and bortezomib (HR 0.695, two-sided *p* value 0.0133).**Error! Bookmark not defined.** For overall survival, the stratified hazard ratio and one-sided stratified log-rank *p* value in favour of lenalidomide, dexamethasone and bortezomib versus lenalidomide and dexamethasone were HR 0.709 (95% CI 0.524–0.959; *p*=0.0125; two-sided *p*=0.0250). Median overall survival was 75 months for lenalidomide, dexamethasone and bortezomib versus 64 months for the lenalidomide and dexamethasone group.**Error! Bookmark not defined.**
Adverse effects (AEs)	The adverse events were fairly well balanced between the two groups. The commonest haematological adverse events (≥ grade 3 and at least possibly

	attributable to treatment) were anaemia, lymphopenia, neutropenia, and thrombocytopenia. The commonest non-haematological adverse events (≥ grade 3 and at least possibly attributable to treatment) were: fatigue, sensory neuropathy, hyperglycaemia, thrombosis or embolism, hypokalaemia, muscle weakness, diarrhoea, and dehydration.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Lenalidomide is already marketed in the UK for the treatment of multiple myeloma and myelodysplastic syndrome.

- 2.5mg blue/white cap, 7=£1142.00; 21=£3426.00.
- 5mg white cap, 7=£1190.00; 21=£3570.00.
- 7.5mg yellow/white cap, 21=£3675.00.
- 10mg blue/yellow cap, 21=£3780.00.
- 15mg blue/white cap, 21=£3969.00.
- 20mg blue/green cap, 21=£4168.50
- 25mg white cap, 21=£4368.00.

Bortezomib is already marketed in the UK for the treatment of multiple myeloma and mantle cell lymphoma. The price of bortezomib is £762 for a 3.5-mg vial and 8 cycles would be £24,396.

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:

☐ Other: ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: ☒ None identified

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