National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: April 2018

Elotuzumab in combination with pomalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma – third line

NIHRIO (HSRIC) ID: 19363 NICE ID: 9788

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 vary but may include bone pain, fractures, body weakness, malaise, bleeding, anaemia and infections. People with MM will experience periods of time without symptoms followed by periods when they return (relapsed MM). Eventually the periods without symptoms will shorten and the illness will become immune to the drugs given to treat it (refractory MM).

Elotuzumab in combination with pomalidomide and low-dose dexamethasone is in development as a treatment option for relapsed and refractory MM. Administered into the vein, elotuzumab belongs to a group of immunotherapy treatments known as monoclonal antibodies. They are designed to recognise and attach to specific proteins found more commonly on the surface of myeloma cells, enabling the immune system to target and destroy them. In combination with oral pomalidomide and low-dose dexamethasone, elotuzumab may offer an additional treatment option for relapsed and refractory MM patients who have tried and failed to respond to current therapies.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Multiple myeloma (relapsed and refractory) – third line and subsequent in those who are refractory to their last treatment

TECHNOLOGY

DESCRIPTION

Elotuzumab (Empliciti) is a first-in-class immunostimulatory agent for the treatment of multiple myeloma (MM). Elotuzumab is an immunostimulatory humanised, IgG1 monoclonal antibody that specifically targets the SLAMF7 (signaling lymphocyte activation molecule family member 7) protein. SLAMF7 is highly expressed on multiple myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer cells, normal plasma cells, and other immune cells including some T cell subsets, monocytes, B cells, and pDCs (plasmacytoid dendritic cells), but is not detected on normal solid tissues or haematopoietic stem cells. Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors enhancing anti-myeloma activity in vitro. Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).[1]

Pomalidomide (Imnovid) is an immunomodulating agent that has shown an anti‑cancer effect in relapsed and refractory multiple myeloma, particularly in patients who have disease that is resistant, or refractory, to previously used anti‑myeloma therapies.[2] Pomalidomide aids the bone marrow in producing normal blood cells, and enhances the ability of immune cells to destroy abnormal cells in the bone marrow.[3]

Dexamethasone, a type of corticosteroid, is used to reduce inflammation and lower the body's immune response.[4] In the phase II clinical trial (ELOQUENT-3; NCT02654132), elotuzumab solution is infused at a dose of 10 mg/kg at cycles 1 and 2 weekly on days 1, 8, 15, 22 and 20 mg/kg at cycle 3 and beyond on day 1.[5]

Elotuzumab is a licenced medicine in the UK/EU and is used in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. The most common adverse reactions (occurring in > 10% of patients) with elotuzumab treatment were infusion related reactions, diarrhoea, herpes zoster, nasopharyngitis, cough, pneumonia, upper respiratory tract infection, lymphopenia and weight decrease.[1]

Elotuzumab in combination with pomalidomide and low-dose dexamethasone does not currently have Marketing Authorisation in the EU for any other indication.

INNOVATION and/or ADVANTAGES

Despite improvements in treatment outcomes with proteasome inhibitors (PIs) and immunomodulatory drugs (iMIDs), most MM patients continue to relapse, and new treatment approaches are needed. Combination therapy may be key to overcoming drug resistance and improving long-term treatment outcomes. Three-drug combinations are emerging for patients with previously treated MM but may be limited by toxic effects. Agents with new mechanisms of action that can be combined with existing therapies without an increase in serious toxicity are needed.[6]

Clinical trials have shown minimal added toxicity when elotuzumab is combined with the iMIDs lenalidomide and thalidomide.[6,7]

If licensed, elotuzumab in combination with pomalidomide and low-dose dexamethasone may offer an additional three-drug treatment option for relapsed and refractory MM patients who have tried and failed to respond on current therapies.

DEVELOPER

Bristol Myers-Squibb, Celgene and AbbVie

REGULATORY INFORMATION and AVAILABILITY/MARKETING PLANS

Elotuzumab is a designated orphan drug in the USA for refractory MM and relapsed MM. Elotuzumab was designated Breakthrough Therapy for refractory MM and relapsed MM by FDA in November 2015.[8]

PATIENT GROUP

BACKGROUND

MM is a rare, incurable disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in disruption of normal bone marrow function, the over-production of monoclonal immunoglobulin and immunosuppression, and osteolysis and end-organ damage.[9] The disease is characterised by cycles of response and progression. With increasing lines of therapy, there is a decreasing duration of response and ultimately development of refractory disease.[10]

Relapsed and refractory MM is defined as a disease which becomes non-responsive or progressive while the patient is on salvage therapy or within 60 days of the last treatment in patients who had achieved a minimal response (MR) or better on prior therapy.[11] The genomic complexity and clonal evolution of MM over the course of treatment are thought to contribute to drug resistance and disease progression.[12]

The cause of MM is unknown, but 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. [13] 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.[13]

Additional risk factors for MM include age, gender, and ethnicity. Cases affecting those under 40 years of age are rare, with men more likely to develop the disease than women. MM is twice as common in black populations compared with white and Asian ethnicities. In early stages, MM may not cause any symptoms or complications and may be diagnosed by routine blood or urine tests.[13] 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.[14]

MM patients experience a variety of disease-related events and subsequent disability, such as bone destruction leading to pain, height reduction and body shape changes, bone marrow failure, renal failure, immunodeficiency, and the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Therapeutic interventions may also produce troublesome side effects and functional impairments. A similar psychosocial burden may be present in caregivers of MM patients, with the role and level of care required evolving as the disease progresses.[15] Health-related quality of life assessment tools that introduce the patient's perspective into the clinical process via standardized self-reports may add an additional dimension to traditional endpoints in both clinical trials and practice.[16]

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. There were 2,928 MM deaths in 2014, accounting for 2% of all cancer mortality in the UK.[17] MM incidence rates are projected to rise by 11% in the UK between 2014 and 2035, to 12 cases per 100,000 people by 2035.[18] 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.[19]

Almost half of patients with MM in England and Wales now survive their disease for at least 5 years, with a third surviving for 10 years or more.[20] Increased life expectancy is mainly due to the availability of novel chemotherapeutic agents, IMiDs and PIs, and the adoption of haematopoietic stem cell transplantation.[21]

The population likely to be eligible to receive elotuzumab in combination with pomalidomide and low-dose dexamethasone could not be estimated from available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Multiple myeloma - lenalidomide (maintenance, post autologous stem cell transplantation) (ID475). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Elotuzumab for multiple myeloma (ID966). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Multiple myeloma (relapsed, refractory) - ixazomib citrate (ID807). Expected February 2018.
- NICE technology appraisal in development. Daratumumab for multiple myeloma (ID933). Expected February 2018.
- NICE technology appraisal in development. Multiple myeloma (newly diagnosed) - lenalidomide (ID474). Expected June 2018.
- NICE technology appraisal in development. Daratumumab with bortezomib for treating relapsed or refractory multiple myeloma (ID974). Expected October 2018.
- NICE technology appraisal in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected October 2018.

- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy (TA171). April 2014.
- 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. Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (TA228). July 2011.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE clinical guideline. Metastatic malignant disease of unknown primary origin in adults: diagnosis and management (CG104). July 2010.
- 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 date of issue to be confirmed.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 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.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/A. April 2013.

OTHER GUIDANCE

Snowden JA, Greenfield DM, Bird JM et al. on behalf of 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[21]

National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017[22]

Palumbo A, Avet-Loiseau H, Oliva S et al. on behalf of the International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015[23]

Bird JM, Owen RG, D'Sa S et al. on behalf of the Haemato-oncology Task Force of the British Committee for Standards in Hameatology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014[24]

Engelhardt M, Terpos E, Klebe M et al. on behalf of 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[25]

CURRENT TREATMENT OPTIONS

Despite recent progress, MM remains incurable and the majority of patients will progress and require treatment. The health and treatment 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. 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.[21]

Treatment options for relapsed and refractory MM which include the novel agents thalidomide, bortezomib and lenalidomide as single-agents or in combination with dexamethasone have shown significant activity in patients with relapsed MM and are generally well tolerated. These agents have set the stage for the development of next-generation IMiDs and PIs (i.e. pomalidomide and carfilzomib in relapsed and/or refractory disease). In general, doublet or triplet regimens are preferred above single agents for optimal effect.[26]

In instances of first relapse, current NICE guidelines recommend the use of:[27]

- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib)
- Bortezomib – only after one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation
- Second autologous stem cell transplant – suitability determined by response to first transplant, number of prior treatments, overall health and fitness, and ranking on Revised International Staging System.

Subsequent relapse treatment may include:

- Lenalidomide in combination with dexamethasone – two or more prior therapies
- Panobinostat in combination with bortezomib and dexamethasone – relapsed and/or refractory, at least two prior therapies including bortezomib and an immunomodulatory agent
- Pomalidomide in combination with low-dose dexamethasone – third or subsequent replace; three previous treatments including both bortezomib and an immunomodulatory agent

EFFICACY and SAFETY

Trial	ELOQUENT-3, NCT02654132, EudraCT-2014-003282-19; elotuzumab in combination with pomalidomide and low-dose dexamethasone; phase II
Sponsor	Bristol-Myers Squibb
Status	Ongoing

Source of Information	Publication[28], trial registry[5]
Location	EU (not incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment and open-label trial
Participants	n=157; aged ≥ 18 years; ≥ 2 prior lines of therapy which must have included at least 2 consecutive cycles of lenalidomide and a proteosome inhibitor alone or in combination; documented refractory or relapsed and refractory multiple myeloma; refractory to proteosome inhibitor and lenalidomide, and to last treatment; relapsed and refractory patients must have achieved at least a partial response to previous treatment with proteosome inhibitor or lenalidomide, or both, but progressed within 6 months, and were refractory to their last treatment; measurable disease at screening; Eastern Cooperative Oncology Group performance status ≤ 2
Schedule	Elotuzumab solution is infused at a dose of 10 mg/kg at cycles 1 and 2 weekly on days 1, 8, 15, 22 and 20 mg/kg at cycle 3 and beyond on day 1. Pomalidomide capsules are administered orally at a dose of 4 mg once daily on days 1 to 21. Patients ≤ 75 years old receive dexamethasone tablets at a dose of 28 mg once daily on days 1, 8, 15, 22 (cycles 1&2) day 1 (cycle 3 and beyond) and also receive intravenous dexamethasone solution at a dose of 8 mg once daily on days 1, 8, 15, 22 (cycles 1&2) day 1 (cycle 3 and beyond) and dexamethasone tablets at a dose of 40 mg once daily on days 8, 15, 22 (cycle 3 and beyond). Those > 75 years old receive dexamethasone tablets at a dose of 8 mg once daily on days 1, 8, 15, 22 (cycles 1&2) day 1 (cycle 3 and beyond) and intravenous dexamethasone solution at a dose of 8 mg once daily on days 1, 8, 15, 22 (cycles 1&2) day 1 (cycle 3 and beyond) and dexamethasone tablets at a dose of 20 mg once daily on Days 8, 15, 22 (cycle 3 and beyond).
Follow-up	Active treatment for 3 or more cycles (28 days/cycle)[28]
Primary Outcomes	• Progression-free survival (PFS); PFS will be defined as the time, in months, from randomization to the date of the first documented tumour progression or death due to any cause [Time Frame: Approximately 14 months]
Secondary Outcomes	• Objective Response Rate [Time Frame: Approximately 14 months] • Overall Survival [Time Frame: Approximately 32 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date April 2019

ESTIMATED COST and IMPACT

COST

The cost of elotuzumab in combination with pomalidomide and low-dose dexamethasone is not yet known.

The NHS Indicative price for elotuzumab (Empliciti) is listed as £1,085.00 for 1 vial of 300 mg powder for concentrate for solution for infusion vials or £1,446.00 for 1 vial of 400 mg powder for concentrate for solution for infusion vials.[29,30]

In the UK, pomalidomide is sold under the brand name Imnovid and the NHS Indicative price for 21 x 4 mg capsules costs £8,884.00.[31]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ 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

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ None identified

OTHER ISSUES

☒ None identified

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