NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Belantamab mafodotin with pomalidomide and dexamethasone for previously treated relapsed/refractory multiple myeloma

Company/Developer	GlaxoSmithKline UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30221	NICE TSID: 11809	UKPS ID: 661985

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Belantamab mafodotin in combination with pomalidomide and dexamethasone is in clinical development for the treatment of relapsed and refractory multiple myeloma (MM) in adult patients who have previously received at least one prior MM therapy. MM is a rare form of cancer characterised by excessive production of abnormal, immature cells (plasma cells) found in the bone marrow. MM is a debilitating and life-threatening disease particularly because it disrupts the normal functioning of the bone marrow, damages the bones and causes kidney failure. Refractory MM is a significant clinical challenge with poor outcomes for patients whose disease has become resistant to the current standard of care. There is therefore need for more treatment options.

Belantamab mafodotin is a monoclonal antibody (a type of protein) that has been designed to stimulate the immune system to attack myeloma cells, and slow progression of the disease. Belantamab mafodotin is administered intravenously. Triplet combination therapies have been shown to be more effective in treatment of relapsed/refractory MM compared to single agents or monotherapies. If licensed, belantamab mafodotin with pomalidomide and dexamethasone will offer an additional treatment option for patients with relapsed and refractory MM, who have previously received at least one prior MM treatment.

Proposed Indication

Belantamab mafodotin in combination with pomalidomide and dexamethasone for treating adult patients with relapsed/refractory multiple myeloma (MM) who have been previously treated with at least 1 line of MM therapy.[1]

Technology

Description

Belantamab mafodotin (belamaf; Blenrep) is a humanised IgG1κ monoclonal antibody conjugated to a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF).[2,3] The antibody has been designed to attach to a protein called B-cell maturation antigen (BCMA), which is present in high levels on the surface of myeloma cells.[3] Belantamab mafodotin binds to cell surface BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis.[2] The cytotoxic molecule kills the cells by interfering with their ability to divide and grow and also stimulates the immune system to attack the myeloma cells, and these actions combined are expected to slow down progression of the disease.[3]

Belantamab mafodotin in combination with pomalidomide and dexamethasone is in clinical development for relapsed/refractory MM patients who have previously received at least 1 prior anti-myeloma therapy. In the phase III clinical trial (DREAMM 8; NCT04484623), patients will receive belantamab mafodotin 2.5 mg/kg (IV) every 4 weeks (Q4W) on Day 1 in Cycle 1 (28-day cycle), followed by belantamab mafodotin 1.9 mg/kg (IV) Q4W on Day 1 in Cycle 2 onwards (28-day cycles); pomalidomide 4 mg (oral) will be administered on Days 1–21 and dexamethasone 40 mg (oral) on Days 1, 8, 15, and 22 in all cycles (28-day cycles).[1,4]

Key Innovation

Relapsed and refractory multiple myeloma (MM) is a significant clinical challenge, with poor outcomes for patients whose disease has become resistant to the current standard of care. Due to the limited options currently available, these patients are often retreated with drugs from the same classes after they relapse.[5] Belantamab mafodotin is a first-in-class, novel therapeutic agent that selectively targets the cancerous cells and elicits an immune response whilst delivering the cytotoxic payload directly to the cancerous cell.[6] Furthermore, triple combination drug regimens are considered a standard of care for patients with relapsed/refractory MM, having demonstrated superior antimyeloma activity to monotherapy and dual combination regimens.[7] The triple combination of belantamab mafodotin plus pomalidomide and dexamethasone has also yielded manageable safety profile.[8]

If licensed, belantamab mafodotin in combination with pomalidomide and dexamethasone would provide a triple combination treatment option with an acceptable benefit-risk profile for patients with relapsed/refractory MM who currently have limited treatment options.

Regulatory & Development Status

Belantamab mafodotin currently has Marketing Authorization in the EU/UK as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[2]

Belantamab mafodotin is also currently in clinical trials for the following key indications:[7]

- As a monotherapy treatment of multiple myeloma in adult patients, who have received at least **two** prior therapies
- In combination with bortezomib and dexamethasone for relapsed/refractory multiple myeloma
- Relapsed or refractory AL amyloidosis

Belantamab mafodotin has also been granted the following regulatory designations/awards:[10,11]

- an orphan drug in the EU in 2017 for the treatment of MM.
- a breakthrough therapy by the US FDA in 2017 to facilitate the development of investigational medicines that have shown clinical promise for conditions where there is significant unmet need.

Patient Group

Disease Area and Clinical Need

Multiple myeloma (MM), also known as myeloma, is a type of bone marrow cancer. Bone marrow is the spongy tissue at the centre of some bones that produces the body's blood cells.[12] The bone marrow produces different types of blood cells.[13] Myeloma develops when DNA is damaged during the development of a plasma cell. This abnormal cell then starts to multiply and spread within the bone marrow.[14] The abnormal plasma cell then begin to proliferate and produce more abnormal cells, known as are myeloma cells.[13] Myeloma affects multiple places in the body where bone marrow is normally active in an adult, such as in the bones of the spine, skull, pelvis, the rib cage, long bones of the arms and legs and the areas around the shoulders and hips.[14] The cause of MM is not well understood however, there is a close link between MM and a condition called monoclonal gammopathy of unknown significance (MGUS). MGUS is where there is an excess of protein molecules, called immunoglobulins, in a patient's blood. Every year, around 1 in every 100 people with MGUS go on to develop MM. Symptoms often include bone pain, bone fractures, spinal cord compression, repeated infections and unusual bleeding.[12]

Myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016-2018). There have been around 6,000 new myeloma cases and around 3,100 myeloma deaths in the UK every year (2016-2018). Over the last decade, myeloma incidence rates have increased by around a tenth (11%) in the UK.[13] In England (2020-21), there were 109,043 finished consultant episodes (FCE) for MM (ICD-10 code: C90.0), with 104,732 hospital admissions that resulted in 94,421 day cases and 67,397 FCE bed days.[15] In England (2017), there were 5,034 patients diagnosed and 2,611 deaths registered where MM and malignant plasma cell neoplasms were the underlying cause.[16] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for myeloma were 82.7% and 52.3% respectively.[17]

Recommended Treatment Options

NICE guidelines recommend the following treatment options for MM after receiving 1 prior treatment:[18]

- Carfilzomib, dexamethasone and lenalidomide for multiple myeloma after one treatment with bortezomib
- Carfilzomib and dexamethasone for multiple myeloma after one treatment
- Bortezomib monotherapy for relapsed multiple myeloma
- Lenalidomide plus dexamethasone for multiple myeloma after one treatment with bortezomib
- Daratumumab, bortezomib and dexamethasone (Cancer Drugs Fund only)

Clinical Trial Information

Trial	**DREAMM 8,** NCT04484623, A Phase III, Multicenter, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Belantamab Mafodotin in Combination With Pomalidomide and Dexamethasone (B-Pd) Versus Pomalidomide Plus Bortezomib and Dexamethasone (PVd) in Participants With Relapsed/Refractory Multiple Myeloma **Phase III:** Recruiting **Location(s):** 7 EU countries, UK USA, Canada and other countries **Primary completion date:** March 2023
Trial Design	Randomized, Parallel Assignment, Open Label
Population	N=300 (estimated); adults 18 years and older; Subjects with a confirmed diagnosis of MM and have been previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen and must have documented disease progression during or after their most recent therapy
Intervention(s)	Belantamab mafodotin 2.5 mg/kg (IV) Q4W on Day 1 in Cycle 1 (28-day cycle) followed by belantamab mafodotin 1.9 mg/kg (IV) Q4W on Day 1 in Cycle 2 onwards (28-day cycles) + pomalidomide 4mg (oral) Days 1 – 21 + dexamethasone 40mg (oral) Days 1, 8, 15, and 22 in all cycles (28-day cycles).[4]
Comparator(s)	Pomalidomide 4 mg (oral) Q3W on Days 1–14 in all cycles (21-day cycles) + bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11 in Cycles 1–8, and Days 1 and 8 in Cycle 9+ (21-day cycles) + dexamethasone 20 mg (oral) on the day of and the day after bortezomib.[4]
Outcome(s)	Primary Outcomes: Progression-free survival (PFS) [time frame: Up to 34 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Belantamab mafodotin is already marketed in the UK; a 100mg powder for concentrate for solution for infusion vials costs £5,707.83.[19]

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Ciltacabtagene autoleucel for treating relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 therapies (GID-TA10905). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma (GID-TA10744). Expected date of issue to be confirmed.

- NICE technology appraisal guidance in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected publication date to be confirmed.
- NICE technology appraisal. Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (TA695). April 2021
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA657). November 2020.
- NICE technology appraisal. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (TA586). June 2019.
- NICE technology appraisal. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). April 2019.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). February 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Bendamustine for relapsed multiple myeloma (all ages). 2020. 200604/P
- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B/15/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: multiple myeloma. 2022.[20]
- British Society for Haematology (BSH) and the UK Myeloma Forum (UKMF). Guidelines on the diagnosis, investigation and initial treatment of myeloma. 2021.[21]
- European Society of Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[22]

Additional Information

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