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HEALTH TECHNOLOGY BRIEFING
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Belantamab mafodotin for relapsed / refractory multiple myeloma – Fourth line

NIHRIO ID	24271	**NICE ID**	10211
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	

Licensing and market availability plans	Currently in phase II clinical trial

SUMMARY

Belantamab mafodotin is in clinical development for the treatment of multiple myeloma (MM) in patients who are refractory or have relapsed to prior treatments. MM is a rare, incurable cancer of the plasma cells in the bone marrow where large amounts of abnormal plasma cells are produced and interfere with the production of red and white blood cells and platelets. People with MM will experience periods of time without symptoms followed by periods when the illness comes back ('relapsed' MM). Eventually the periods without symptoms will shorten and the illness will become immune to the drugs given to treat it ('refractory' MM).

Belantamab mafodotin is a first-in-class therapy delivered via intravenous infusion. This medicine is an antibody drug conjugate comprising a B cell maturation antigen (BCMA)-targeting monoclonal antibody that delivers a cytotoxin (cysMMAF) to abnormal plasma cells, which interferes with the cell's ability to divide and grow and encourages the immune system to attack the affected cells, slowing the progression of the disease. If licensed, belantamab mafodotin has the potential to improve outcomes in patients that have already received prior treatments but their myeloma has come back.

PROPOSED INDICATION

Treatment of relapsed and refractory multiple myeloma in adult patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody[a]

TECHNOLOGY

DESCRIPTION

Belantamab mafodotin (Anti-BCMA antibody drug conjugate; J6M0; GSK2857916) is a humanised monoclonal antibody. The abnormal immature plasma cells in patients with multiple myeloma produce a protein on their surface called B-cell maturation antigen (BCMA). This medicine is made up of maleimidocaproyl monomethyl auristatin F (MMAF), a cytotoxic molecule, which is attached to a monoclonal antibody that has been designed to recognise and attach to BCMA. When the medicine is given to the patient, it is expected to bind to BCMA on the myeloma cells and deliver MMAF into the cells. Once inside the myeloma cells, MMAF kills them by interfering with their ability to divide and grow. In addition, by attaching to the myeloma cells the medicine is expected to encourage the immune system to attack them and thereby slow the progression of the disease.[1]

Belantamab mafodotin is currently in clinical development for the treatment of relapsed/refractory multiple myeloma. In the phase II clinical trial (NCT03525678) conducted in patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent, and anti-CD38 antibody, and who have demonstrated disease progression on the last therapy, belantamab mafodotin (2.5 mg/kg or 3.4 mg/kg) is administered via 1-hour intravenous infusion once every 3 weeks until disease progression.[2]

INNOVATION AND/OR ADVANTAGES

Belantamab mafodotin is a first-in-class therapy that consists of an afucosylated antibody drug conjugate (ADC) that is conjugated to the toxin monomethyl auristatin-F (MMAF). Belantamab mafodotin targets BCMA via two main mechanisms of action: 1) enhanced antibody-dependent cytotoxicity (ADCC) via afucosylation of the monoclonal antibody, and 2) potent toxin delivery via the ADC component. This medicine may be of significant benefit for patients with multiple myeloma as the first time in human study indicated that patients whose disease came back after several previous treatments responded to treatment with this medicine.[1]

The novel mode of action of belantamab mafodotin is innovative especially for the initial 4th line indication as patients have exhausted all current therapies.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Belantamab mafodotin is not licensed for any other cancer indications in the EU/UK.

Belantamab mafodotin monoclonal antibody has the following regulatory designations/ awards:

- An orphan drug in the EU in 2017 for multiple myeloma.[1]

[a] Information provided by GlaxoSmithKline UK Ltd

- A PRIME status awarded by the EMA in October 2017 for the treatment of relapsed and refractory multiple myeloma in adult patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody.[3]

PATIENT GROUP

DISEASE BACKGROUND

Multiple Myeloma (MM) is an incurable orphan disease characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, and immunosuppression, as well as osteolysis and end-organ damage.[4] MM can affect multiple organs and their respective systems, including blood, bones, kidney and immune system.[5] Although the survival rates for MM have increased with the introduction of several new drugs with novel mode of action, patients ultimately relapse and it remains incurable.[6]

Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Patients who never achieve at least a minimal response (i.e. at least a 25% reduction in M protein) to initial induction therapy and progress while on therapy are defined as primary refractory.[7] Additional mutations and genetic alterations that are present in relapsed or progressive MM make the disease more resistant to available agents, resulting in reduced remission or response to each line of salvage therapy, and ultimately leads to the development of relapsed/refractory MM.[8] The tumour behaviour at the second relapse and beyond, tends to be shorter due to this more aggressive tumour activity.[9]

The origin of MM is 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 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, and sub classifications of MGUS have allowed identification of patients with much higher rates of progression to frank MM. 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]

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]

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 such as an abnormal elevation in serum immunoglobulin levels.[4] Other features of MM are often denoted by the "SLiM CRAB" criteria, which include can include S= $\geqslant$ Sixty-percent ($\geqslant$ 60%) clonal BM plasma cells; Li=serum free Light chain ratio involved:uninvolved $\geqslant$ 100; M=>1 focal lesion ($\geqslant$ 5 mm each) detected by MRI studies; H=hyperCalcemia, R=Renal dysfunction, A=Anaemia and B=Bone disease.[14] Symptoms associated with these SLiM CRAB criteria 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] 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.[15]

In many relapse trials the occurrence of any grade treatment-related adverse events is approximately 50% and serious adverse events (SAE) 20%. Treatment-related adverse events are a frequent cause of premature discontinuation, which influences outcome.[6] Patients often have pronounced symptoms and substantially reduced health-related quality of life (HRQoL). Around 80% of patients experience skeletal destruction, approximately 73% will have anaemia at diagnosis and about 30% of patients present with renal insufficiency. [16]

CLINICAL NEED AND BURDEN OF DISEASE

Myeloma is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases (2016). In females in the UK it is the 18th most common cancer (1% of all new female cancer cases). In males in the UK, myeloma is the 16th most common cancer (2% of all new male cancer cases).

The European age-standardised incidence rate of myeloma in England was 9.3 per 100,000 population in 2016.[17] In England in 2017 there were a total of 5,034 newly diagnosed cases of multiple myeloma, of which approximately 58% were in males. In the same year a total of 2,611 deaths due to multiple myeloma were recorded for England (ICD-10 code C90).[18] For the whole of the UK, the European age-standardised incidence rates of myeloma are expected to increase from 5,500 observed cases in 2014 (equivalent to 11.12 per 100,000 persons) to 8,889 by 2035 (equivalent to 12.38 per 100,000 persons).[19]

In England, for people aged 15 to 99 years old that have been diagnosed with myeloma between 2012 and 2016 and followed up in 2017, the age-standardised one and five year survival is 82.1% and 51.7% respectively.[20]

The Hospital Episodes Statistics for England 2017/2018 recorded 139,605 finished consultant episodes, 134,697 hospital admissions, 96,137 bed days and 123,651 day cases for primary diagnosis multiple myeloma and malignant plasma cell neoplasms (ICD 10 code C90).[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The choice of therapy in the relapsed setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).[22]

The length of the prior remission duration is a critical component in making a choice of salvage therapy. The depth of the first response, remission duration of the patient's prior therapies, and tumour burden at relapse can suggest the aggressiveness of the relapse.[23]

CURRENT TREATMENT OPTIONS

Lenalidomide in combination with dexamethasone is recommended for the treatment of multiple myeloma in transplant-eligible patients who have received at least two prior therapies.[24,25]

The following are recommended as subsequent (post-second line) therapies for treating multiple myeloma in transplant in-eligible patients:[24-29]

- daratumumab monotherapy
- ixazomib, with lenalidomide and dexamethasone
- pomalidomide, in combination with low-dose dexamethasone
- panobinostat in combination with bortezomib and dexamethasone
- lenalidomide in combination with dexamethasone

PLACE OF TECHNOLOGY

If licensed, Belantamab mafodotin will offer a treatment option for individuals with relapsed/refractory multiple myeloma who currently have limited treatment options having failed on prior therapies.

CLINICAL TRIAL INFORMATION

Trial	**NCT03525678, Eudra CT 2017-004810-25; aged 18 years or older; frozen versus lyophilized GSK2857916; phase II**
Sponsor	GlaxoSmithKline
Status	Ongoing
Source of Information	Trial registry[2]
Location	Five EU countries (incl UK), USA, Canada and Australia
Design	Randomised, open label
Participants	N=223; aged 18 years and older; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; histologically or cytologically confirmed diagnosis of multiple myeloma as defined according to International Myeloma Working Group
Schedule	Randomized in 1:1 ratio to receive 2.5 milligram per kilogram (mg/kg) or 3.4 mg/kg frozen liquid belantamab mafodotin via intravenous infusion pump for once in every 3 weeks until disease progression or unacceptable toxicity.
Follow-up	Two years
Primary Outcomes	Overall response rate (ORR) defined as the percentage of subjects with a confirmed partial response (PR) or better [Time frame: every 3 weeks up to 2 years)
Secondary Outcomes	Time frame: pre-dose within 30 minutes prior to start of infusion (SOI) and end of Infusion (EOI) on cycle (C)1; pre-dose, 2 hours after SOI on C2, C6, C9, and C12 and at EOI; every 6 subsequent cycles at pre-dose and at EOT • Area under the curve (AUC) of belantamab mafodotin blood samples will be collected at indicated time points for analysis of AUC • Maximum plasma concentration (Cmax) of belantamab mafodotin • Time of occurrence of Cmax (Tmax) of belantamab mafodotin

	• Terminal phase half-life (T1/2) of belantamab mafodotin Time frame: every 3 weeks up to 2 years • Clinical benefit rate (CBR) CBR is defined as the percentage of subjects with a confirmed minimal response (MR) or better according to the 2016 IMWG IRC • Duration of response (DoR) DoR is defined as the time from first documented evidence of PR or better until the earliest date of documented PD per IMWG; or death due to PD occurs among subjects who achieve an overall response, i.e., confirmed PR or better • Time to response Time to response is defined as the time between the date of first dose and the first documented evidence of response (PR or better). • Progression free survival Progression free survival is defined as the time from first dose until the earliest date of documented disease progression (PD) per IMWG, or death due to any cause • Time to progression Time to progression is defined as the time from first dose until the earliest date of documented PD per IMWG, or death due to PD • Overall survival Overall survival is defined as the time from first dose until death due to any cause • Number of subjects with abnormal hematology parameters Laboratory assessment for hematology parameters will include Platelet count, hemoglobin (Hgb), Red blood cell (RBC) count, hematocrit, reticulocyte count, RBC indices like mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). White blood cell (WBC) count with differential will include neutrophils, lymphocytes, monocytes, eosinophils and basophils • Number of subjects with abnormal clinical chemistry parameters Laboratory assessment for clinical chemistry parameters will include blood urea nitrogen (BUN), potassium, calcium, sodium, creatinine, glucose, magnesium, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphate, total protein, total and direct bilirubin, albumin, uric acid, lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT), Creatine kinase (CK), total bicarbonate, albumin/ creatinine ratio, Estimated glomerular filtration rate (eGFR), chloride, and phosphorus. • Number of subjects with abnormal physical examination parameters Physical examination parameters will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. • Number of subjects with abnormal systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessment SBP and DBP will be measured after 5 minutes rest

	• Number of subjects with abnormal pulse rate Pulse rate will be measured after 5 minutes rest • Number of subjects with abnormal body temperature Temperature will be measured after 5 minutes rest • Number of subjects with symptomatic AEs measured by Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. It provides systematic and flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. • Number of subjects with symptomatic AEs measured by National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. • Number of subjects with symptomatic AEs measured by Ocular Surface Disease Index (OSDI) The OSDI is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning. <u>Time frame: up to 2 years</u> • Number of subjects with adverse events (AEs), serious AEs (SAEs) and AEs of special interest (AESI) An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. A SAE is defined as any untoward medical occurrence that at any dose may result in death due to PD, is life-threatening, may require hospitalization or prolongation of existing hospitalization, result in persistent disability/incapacity, or may led to any congenital anomaly or birth defect. AESI for belantamab mafodotin are corneal events, thrombocytopenia and infusion related reactions. • Number of subjects with abnormal ocular findings Ocular examination for the subjects will include procedures for corrected visual acuity, current glasses, pupillary examination, extra ocular muscular movements, intra-ocular pressure, examination of tear film, and examination of cornea. • Incidence and titers of anti-drug antibodies (ADAs) Blood samples will be collected at indicated time points for analysis of ADAs using electrochemiluminescent immunoassay <u>Time Frame: Every 6 weeks up to 2 years</u> • Change in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) score

	The EORTC QLQ-C30 is a 30-item questionnaire containing both single and multi-item measures. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/ Quality-of-Life (QoL) scale, and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). The scores ranges from 0-100, a high score for functional scales and for Global Health Status/QoL represent better functioning ability or Health-Related Quality-of-Life (HRQoL), whereas a high score for symptom scales and single items represents significant symptomatology. • Change in EORTC QLQ- 20-item Multiple Myeloma module (MY-20) score The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in subjects with MY. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes.
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Estimated primary study completion date reported as June 21, 2019. Estimated final study completion date reported as June 19th 2020.

ESTIMATED COST

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma [ID1620] (GID-TA10491). Expected publication date TBC.
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477] (GID-TA10448). Expected publication date TBC.
- NICE technology appraisal in development. Daratumumab in combination for untreated multiple myeloma when stem cell transplant is unsuitable [ID1492] (GID-TA10441). Expected publication date TBC.
- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma [ID1535] (GID-TA10412). January 2021.

- NICE technology appraisal guidance. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
- NICE technology appraisal guidance. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal guidance. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal guidance. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal guidance. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal guidance. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal guidance. Pomalidomide for relapsed and refractory multiple myeloma previously treated with lenalidomide and bortezomib (TA338). March 2015.
- NICE technology appraisal guidance. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). Updated October 2018.

NHS ENGLAND (POLICY/COMMISSIONING) 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 (HSCT) (All Ages): Revised. B04/P/a
- NHS England. 2013/14. NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a
- NHS England. 2013/14. NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children). B04/S/b
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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.[30]
- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[22]
- National Comprehensive Cancer Network. American NCCN Guidelines: Version 3 – NCCN Evidence Blocks: Myeloma Therapy. 2017.[31]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015.[32]
- 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.[33]

ADDITIONAL INFORMATION

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