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Health Technology Briefing
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Idecabtagene vicleucel for treating relapsed or refractory multiple myeloma after 2 therapies

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28246	NICE ID: 10330	UKPS ID: 663431

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Idecabtagene vicleucel is in clinical development for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received at least 2 but no greater than 4 prior MM regimens. MM is a rare, incurable blood cancer that forms in the plasma calls in the bone marrow, inside some of the large bones of the body. The cancerous cells build up and interfere with production of red and white blood cells, and platelets. MM is an incurable disease so patients go through periods of being symptom-free following treatment before the illness returns/ relapses and can no longer be treated with the same therapies (becomes resistant/ refractory). Patients often go through the cycle many times and new treatment options could increase the lengths overall survival.

Idecabtagene vicleucel contains the patient's own T-cells (a type of white blood cell) that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). CAR can attach on the surface of cancer cells and then kill the cells, thereby helping to clear the cancer from the body. Idecabtagene vicleucel is given as a single intravenous infusion. If licensed, idecabtagene vicleucel would increase the treatment options for adult patients with relapsed and refractory MM who have received at least 2 but no greater than 4 prior MM regimens.

Proposed Indication

For the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received at least 2 but no greater than 4 prior MM regimens.[1]

Technology

Description

Idecabtagene vicleucel (Ide-cel; bb2121; Abecma) is a chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen (BCMA).[2,3] BCMA, also known as tumour necrosis factor receptor superfamily member 17 (TNFRSF17), is a cell surface receptor expressed on the surface of normal and malignant plasma cells. It regulates the proliferation and survival, as well as the maturation and differentiation of B-cells into plasma cells, also prolonging the survival of long-lived plasma cells.[4,5] In MM, the expression of BCMA is significantly increased on malignant plasma cells over the normal plasma cells, thereby protecting the myeloma cells from apoptosis (programmed cell death) by the upregulation of antiapoptotic proteins. BCMA also induces the expression of immunosuppressive molecules such as programmed death-ligand 1(PD-L1) in MM cells.[6]

Idecabtagene vicleucel is currently in clinical development for the treatment of adult patients with relapsed and refractory MM who have received at least 2 but no greater than 4 prior MM regimens.[7] In the phase III clinical trial (KarMMa-3; NCT03651128), participants will be infused with idecabtagene vicleucel autologous CAR T-cells at a dose ranging from 150 - 450 x 10^6 CAR T-cells after receiving lymphodepleting chemotherapy.[1]

Key Innovation

Treatment of MM has involved the use of conventional and novel therapeutics, either alone or in combination with transplantation. However, recurrence of the disease due to drug resistance as well as adverse effects from these therapies remains a significant obstacle.[5]

Multiple innovative BCMA-targeted therapeutics, including CAR T-cell therapies, are under active clinical development. Treatment with idecabtagene vicleucel has resulted in rapid and sustained tumour elimination and 100% survival in a mouse model of human MM.[4] Idecabtagene vicleucel induced responses in a majority of heavily pretreated patients with refractory and relapsed myeloma in a phase II trial (NCT03361748); minimal residual disease (MRD)– negative status was achieved in 26% of treated patients.[8]

Idecabtagene vicleucel is an advanced therapy medicinal product (ATMP) within the definition of a gene therapy medicine.[7,9]

If approved, idecabtagene vicleucel would offer an additional treatment option for adult patients with relapsed and refractory MM.

Regulatory & Development Status

Idecabtagene vicleucel has conditional Marketing Authorisation in the EU for the treatment of adults with relapsed and refractory MM who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody.[10]

Idecabtagene vicleucel has the following designations:[11,12]

- an orphan drug in the EU in 2017 for the treatment of MM.
- a PRIME status for treatment of relapsed and refractory MM patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, by the EMA in November 2017 (previously granted).

Patient Group

Disease Area and Clinical Need

Multiple myeloma (MM) is a type of bone marrow cancer that is 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.[13,14] MM can affect multiple organs and systems including the bones, kidneys, blood and immune system.[15] Relapsed and refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.[16] Risk factors for MM include age, gender and ethnicity.[17] Other risk factors include having a family history of the disease, having taken immunosuppressants and past exposure to radiation.[18] MM 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.[19]

There are around 6,000 new MM cases in the UK every year, that's 16 every day (2016-2018). It is the 19th most common cancer in the UK, accounting for 2% of all new cancer cases. Incidence rates in the UK are highest in people aged 85 to 89.[20] According to the 2020-21 Hospital Episodes Statistics data, there were 107,457 finished consultant episodes (FCEs), 103,209 admissions and 66,906 FCE bed days for MM (ICD-10 code C90.0).[21] There are around 3,100 MM deaths in the UK every year, that's more than 8 every day (2016-2018). Mortality rates for MM are projected to fall by 17% in the UK between 2014 and 2035, to 5 deaths per 100,000 people by 2035.[22]

Recommended Treatment Options

Treatment for relapsed MM depends on how long the patient was in remission for, the previous treatment received and the general health of the patient. Treatment options usually involve the use of targeted cancer drugs; a combination of chemotherapy drugs, with or without targeted cancer drugs; and a steroid.[23] Standard drug classes for treating relapsed and refractory MM include proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 monoclonal antibodies (mAbs).[24]

NICE guidelines recommend the use of:[25-29]

- Lenalidomide plus dexamethasone for people who have received two or more prior therapies for relapsed or refractory MM
- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent
- Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory MM in adults who have had 2 or 3 lines of therapy

- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last treatment, only if they have daratumumab after 3 treatments
- Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory MM in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if they have had 3 previous lines of treatment

Clinical Trial Information	
Trial	**KarMMa-3**, NCT03651128, EudraCT 2018-001023-38; A Phase 3, Multicentre, Randomised, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Regimens in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) **Phase III** – Ongoing **Locations**: 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** May 2022
Trial Design	Multicentre, randomised, parallel assignment, open label
Population	N=381 (estimated); aged 18 years and older; Subjects with a documented diagnosis of MM and have received at least 2 but no greater than 4 prior MM regimens
Intervention(s)	Idecabtagene vicleucel autologous CAR T-cells will be infused at a dose ranging from 150 - 450 x 10^6 CAR+ T-cells after receiving lymphodepleting chemotherapy.
Comparator(s)	One of following regimens dependent on the subject's most recent anti-myeloma treatment regimen: • Daratumumab (DARA) in combination with pomalidomide (POM) and low-dose dexamethasone (dex) (DPd) OR • DARA in combination with bortezomib (BTZ) and low-dose dex (DVd) OR • Ixazomib (IXA) in combination with lenalidomide (LEN) and low-dose dex (IRd) OR • Carfilzomib (CFZ) in combination with low-dose dexamethasone (Kd) OR • Elotuzumab (ELO) in combination with POM and low-dose dexamethasone (EPd)
Outcome(s)	Primary outcome measure: • Progression-free Survival (PFS) [Time Frame: Minimum of 5 years from randomization] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of idecabtagene vicleucel is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies (ID2701). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Elotuzumab for multiple myeloma (ID966). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies (ID1442). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Pelareorep for treating relapsed or refractory multiple myeloma (ID1028). Expected publication date to be confirmed
- NICE technology appraisal guidance in development. Pembrolizumab for previously treated multiple myeloma (ID1139). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Plitidepsin in combination with dexamethasone for treating relapsed or refractory multiple myeloma (ID1081). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Selinexor with bortezomib and low dose dexamethasone for treating relapsed or refractory multiple myeloma (ID3797). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma (ID3862). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (CDF review of TA505) (ID1635). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma (ID3816). Expected publication date 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 October 2022.
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- NICE technology appraisal. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658). November 2020.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA657). November 2020.
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
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- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.

- NICE guideline. Myeloma: diagnosis and management (NG35). October 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 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.
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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

Other Guidance

- British Society for Haematology (BSH) and the UK Myeloma Forum (UKMF). Guidelines on the diagnosis, investigation and initial treatment of myeloma. 2021.[30]
- European Society of Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[31]
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: multiple myeloma, version 3. 2020.[32]
- American Society of Clinical Oncology. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. 2019.[33]
- NHS England. Manual for prescribed specialist services. Chapter 29: blood and marrow transplantation services (adults and children); Chapter 105: specialist cancer services (adults). 2018/19.[34]
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