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Health Technology Briefing
January 2022

Teclistamab for previously treated relapsed or refractory multiple myeloma

Company/Developer	Janssen-Cilag Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30599	NICE ID: 10734	UKPS ID: 662561

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Teclistamab is in clinical development for the treatment of relapsed or refractory multiple myeloma (MM) in patients who have received at least three prior lines of therapy. 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.

Teclistamab is a novel type of cancer medicine that can bind to a molecule found on the abnormal MM cells and the patient's immune cells, to induce the killing of the cancer cells. Teclistamab is administered by subcutaneous injection which allows for higher doses to be delivered to the patient while limiting adverse events from toxicities. If licensed teclistamab will offer a new treatment option for patients with relapsed or refractory MM, who have already received at least three types of treatment.

Proposed Indication

Treatment of patients with relapsed or refractory multiple myeloma (MM).[1]

Technology

Description

Teclistamab (JNJ-64007957) is a humanised monoclonal antibody that targets the B-cell maturation antigen (BCMA), a member of the tumour necrosis factor family of receptors which is highly expressed on the plasma cell of MM patients.[2] Teclistamab also binds to the CD3 protein of T cells in the immune system, attaching BCMA and CD3 together to activate an immune response against the MM cells.[3,4]

Teclistamab is in clinical development for relapsed/ refractory MM patients who have previously received greater than or equal to 3 prior lines of therapy including one proteasome inhibitor (PI), one immunomodulatory drug (IMiD), and one anti-CD38 monoclonal antibody (mAb).[1] In the phase II clinical trial (NCT04557098), teclistamab will be administered subcutaneously (SC) at the recommended phase 2 dose (RP2D) of 1500 µg/kg once per week, after 60 µg/kg and 300 µg/kg step-up doses.[1,5]

Key Innovation

The development of novel agents for treatment of MM has begun to improve the overall survival rates to become more favourable, as patients can now be managed at various relapse stages with more complex regimens. MM remains a fatal and incurable form of cancer due to the eventual emergence of drug-resistance seen with all available treatments.[6] Subcutaneous administration of teclistamab allows for a higher dose to be administered weekly than with other methods such as intravenous infusions, with no dose-limiting toxicities at the RP2D.[5]

Teclistamab is the only bispecific antibody targeting both BCMA and CD3 on T cells. Results from preclinical studies demonstrate that teclistamab induces T-cell mediated cytotoxicity and the killing of MM cells through the recruitment and activation of CD3-expressing T-cells.[2]

If licensed, teclistamab would provide a new treatment option for patients with relapsed/ refractory MM whose prior treatment regimens have included a PI, a IMiD, and a mAb.[1]

Regulatory & Development Status

Teclistamab does not currently have marketing authorisation in the EU/ UK for any indication.

Teclistamab is in phase II and III clinical development as a monotherapy and in combination in various populations of patients with relapsed or refractory MM.[7,8]

Teclistamab was granted the following regulatory designations/awards:

- Orphan drug by the EMA in October 2020 for the treatment of MM. [3]
- PRIME status by the EMA in January 2021 for the treatment of adult patients with relapsed or refractory MM, who previously received ≥3 prior lines of therapy.[9]
- Breakthrough therapy by the US FDA in June 2021.[4]

Patient Group

Disease Area and Clinical Need

Multiple myeloma (MM) is a type of cancer that develops in the plasma cells of the bone marrow, causing an abnormal build-up of cells and paraprotein, damaging the bones and affecting the production of healthy blood cells.[10,11] MM is an incurable relapsing-remitting cancer, meaning there are periods of symptoms and/or complications which require treatment, followed by periods of remission or plateau where there are no symptoms and does not require treatment. Most patients develop multiple drug resistance, often through mutation or alteration in the expression of the drug target, resulting in the need to discover and target novel pathways.[12] Triple-class refractory MM is one in which the MM is resistant to all three classes of standard myeloma therapies.[13] There is no known cause of MM in most cases, but there are several known risk factors. Prevalence is highest in men and is most often diagnosed in adults around the age of 70.[10] Race and weight can also be risk factors, as well as immune conditions such as HIV and monoclonal gammopathy of undetermined significance (MGUS).[14] Every year 1 in 100 people with MGUS develop MM, and people with a family history of MGUS or MM are more likely to develop MM, showing a genetic influence.[10] MM is often asymptomatic in the early stages and is often found when patients are undergoing routine tests, but it progresses to affect multiple organ systems.[10,14] In later stages, symptoms include persistent bone pain, fatigue and weakness, shortness of breath, unexplained bruising, recurrent infections and kidney damage.[10,15]

MM is the 19th most common cancer in the UK and accounts for 15% of new blood cancer diagnosis and 2% of all cancer cases.[11,16] Each year in the UK there are approximately 6,000 new MM cases, with around 3,100 deaths (2016-18). The five-year survival rate in England is 52.3%, dropping to 29% survival over 10 years (2013-17).[16] In England (2020-21), there were 107,457 finished consultant episodes (FCE) for MM (ICD-10 code: C90.0), with 103,209 hospital admissions that resulted in 92,913 day cases and 66,906 FCE bed days.[17]

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.[18]

NICE guidelines recommend the following treatment options for relapsed or refractory MM:[19]

- Ixazomib, with lenalidomide and dexamethasone is recommended for patients who have already received 2 or 3 lines of therapy.
- Panobinostat in combination with bortezomib and dexamethasone is recommended for adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.
- Lenalidomide in combination with dexamethasone is recommended in people who have received 2 or more prior therapies.
- Isatuximab, plus pomalidomide and dexamethasone, is recommended for 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.
- Daratumumab monotherapy is recommended for treating relapsed and refractory MM in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

- Pomalidomide, in combination with low-dose dexamethasone, is recommended for treating MM in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib.

Clinical Trial Information	
Trial	**MajesTEC-1;** NCT04557098, 2016-002122-36; A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects With Relapsed or Refractory Multiple Myeloma **Phase II** - Ongoing **Location(s):** 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** April 2023
Trial Design	Single group assignment, open label
Population	N= 192 (estimated); Subjects with MM who have received at least 3 prior MM treatment lines of therapy; aged 18 years and older.
Intervention(s)	Teclistamab (SC) at a RP2D of 1.5 mg/kg once weekly.[20]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Overall Response Rate (ORR) [Time Frame: Up to 2.9 years] See trial record for full list of other outcomes.
Results (efficacy)	At the median follow-up of nearly eight months, an ORR of 62 percent (93/150; 95 percent Confidence Interval [CI], range, 53.7–69.8) was observed; ORR was consistent regardless of cytogenetic risk or extent of prior therapy refractoriness. At the clinical cut-off, median duration of response was not reached and 88 percent (82/93) of responders were alive and continuing treatment. Study results suggest that responses to teclistamab were durable and deepened over time. Among patients who responded, the median time to first confirmed response was 1.2 months (range 0.2-5.5 months). Fifty-eight percent of patients receiving teclistamab achieved a very good partial response (VGPR) or better; 29 percent achieved a complete response (CR) or better; and 21 percent achieved a stringent complete response (sCR). By intent to treat, 25 percent of patients (37/150) achieved MRD negativity at a threshold of 10^{-5} (95 percent CI, range, 18.0–32.4). In patients who achieved CR or better, the MRD negativity rate was 42 percent. The progression-free survival (PFS) rate at 9 months was 59 percent (95 percent CI, range, 48.8–67.0). Median overall survival (OS) was not reached.[20]
Results (safety)	Teclistamab had a tolerable safety profile, and no patients required a dose reduction. The most common nonhematologic adverse events (AEs) were cytokine release syndrome (72 percent; all grade 1/2 except for 1 grade 3 event that fully resolved; all resolved with no treatment discontinuation), injection site erythema (26 percent; all grade 1/2) and fatigue (25 percent; 2 percent grade 3/4). The most common hematologic AEs were neutropenia (66 percent; 57

	percent grade 3/4), anaemia (50 percent; 35 percent grade 3/4) and thrombocytopenia (38 percent; 21 percent grade 3/4). Five patients (3 percent; all grade 1/2) developed immune effector cell-associated neurotoxicity syndrome (ICANS) all resolved without discontinuation.[20]

Estimated Cost

The cost of teclistamab 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 January 2023.
- NICE technology appraisal guidance in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected publication date October 2022.
- 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 March 2022.
- NICE technology appraisal guidance in development. Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma (ID3816). Expected publication date February 2022.
- NICE technology appraisal. Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (TA695). April 2021.
- 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.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- 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
- NHS England. Clinical Commissioning Policy: Intrathecal Drug Delivery for Cancer Pain. 2015. D08/P/b
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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.[21]
- European Society of Medical Oncology (ESMO). Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[22]
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: multiple myeloma, version 3. 2020.[23]
- American Society of Clinical Oncology. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. 2019.[24]
- 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.[25]
- NHS England. National chemotherapy algorithms – multiple myeloma. 2015.[26]
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A report from IMWG. 2015.[27]

Additional Information

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