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HEALTH TECHNOLOGY BRIEFING
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JNJ-68284528 for relapsed or refractory multiple myeloma

NIHRIO ID	28293	**NICE ID**	10388
Developer/Company	Janssen-Cilag Ltd.	**UKPS ID**	655171

Licensing and market availability plans	Currently in phase I/II/III clinical trials

SUMMARY

JNJ-68284528 is in clinical development for the treatment of relapsed and/or refractory multiple myeloma (MM). MM is a rare, incurable cancer of the plasma cells in the bone marrow. Abnormal plasma cells interfere with the production of red and white blood cells as well as platelets, causing symptoms such as bone pain and fragility, weakness, unusual bleeding (from the gums and nose, as well as heavy periods) and eventually kidney damage. In the early stages, MM is symptomless, then, as disease progresses, patients experience periods of time without symptoms followed by periods where the symptoms return (relapsed MM). Eventually the periods without symptoms will shorten and the illness will become immune to the treatment (refractory MM). As most patients experience serial relapse to existing treatments, there is a need for new treatment options.

JNJ-68284528 is a type of gene therapy that targets a protein called BCMA (B cell maturation antigen) which is expressed on B-cells (a type of immune cell). Binding of JNJ-68284528 to BCMA prevents B-cell maturation and differentiation into plasma cells. JNJ-68284528 is administered as an intravenous infusion. Early stage clinical trials (phase II) have demonstrated both safety and efficacy of JNJ-68284528 in patients with relapsed/refractory MM and could therefore provide an additional treatment option for patients with the disease.

PROPOSED INDICATION

Relapsed and/or refractory multiple myeloma.[1]

TECHNOLOGY

DESCRIPTION

JNJ-68284528 (JN-4528, LCAR-B38M) is a preparation of autologous T lymphocytes that are transduced, *ex vivo*, with a lentiviral vector expressing a chimeric antigen receptor (CAR). The CAR contains two bispecific anti-B-cell maturation antigen (BCMA) variable fragments of llama heavy-chain murine antibodies, which are fused to the signalling domain of 4-1BB (CD137). Thus, JNJ-68284528 has potential immune-stimulating and antineoplastic activities. The antigen-binding region of the CAR is a non-scFv structure targeting two distinct regions of BCMA. Upon intravenous administration back into the patient, the autologous BCMA-targeted CAR T cells JNJ-68284528 are directed to cells expressing BCMA, bind to two different epitopes on BCMA and induce selective toxicity in BCMA-expressing tumour cells. BCMA, a tumour-associated antigen (TAA) and a receptor for both a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), is a member of the tumour necrosis factor receptor superfamily (TNFRSF) and plays a key role in plasma cell survival. BCMA is overexpressed on malignant plasma cells.[2]

In the phase III clinical trial (NCT04181827), patients were administered one cycle of bridging therapy (bortezomib and dexamethasone OR daratumumab, pomalidomide and dexamethasone (DPd), followed by a conditioning regimen (cyclophosphamide 300mg/m^2 IV and fludarabine 30mg/m^2 IV daily for 3 days) and JNJ-68284528 infusion at 0.75 x 10^6 CAR-positive viable T cells/Kg, as a single dose, with or without further cycles of bridging therapy.[1]

INNOVATION AND/OR ADVANTAGES

As multiple myeloma (MM) is an incurable malignancy, new approaches to treatment are needed. T-cell therapies are a promising approach for treating MM, with a mechanism of action different than those of standard MM treatments. Chimeric antigen receptors (CARs) are fusion proteins incorporating antigen-recognition domains and T-cell signalling domains. T-cells genetically engineered to express CARs can specifically recognise antigens. Success of CAR-T cells against leukaemia and lymphoma has encouraged the development of CAR-T therapies for MM. BCMA is expressed by normal and malignant plasma cells. CAR-Ts targeting BCMA have demonstrated significant anti-myeloma activity in early clinical trials. Toxicities in these trials, including cytokine release syndrome, have been similar to toxicities observed in CAR-T trials for leukaemia.[3]

In the phase 1b-2 trial, CARTITUDE-1 (NCT03548207), patients with an average of five prior treatment regimens were treated with JNJ-68284528 at 0.73x10^6 cells/Kg. A hundred percent of patients achieved a response at a median six-month follow-up and the overall response rate was 69% for a complete response and 86% achieving a very good partial response or better. In addition, 100 percent of evaluable patients achieved early minimal residual disease-negative disease status at day 28 post-infusion. At the six-month follow-up, 27 of 29 patients were progression-free.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In February 2020 JNJ-68284528 was given orphan designation by the European Medicines Agency (EMA) (EU/3/20/2252) and PRIME designation in March 2019. [5,6] In December 2019, JNJ-68284528 was granted breakthrough therapy designation and in February 2019 was granted orphan drug designation by the US Food and Drug Administration (FDA).[7]

In the phase 1b/2 study, CARTITUDE, the most common adverse events (AEs) observed were cytokine release syndrome (CRS) (93%); neutropenia (93%); anaemia (86%); and thrombocytopenia (86%). In patients who experienced grade 3 and above AEs (25%); the most common were neutropenia (93%); thrombocytopenia (69%); and anaemia (55%).[4]

This product is not licensed for any other cancer indications in the EU/UK.

PATIENT GROUP

DISEASE BACKGROUND

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.[8,9] MM can affect several bones in the body such as the spine, skull, pelvis and ribs, as well as the blood, kidney and immune system. [8,10]

In the early stages, MM does not cause any symptoms and is often diagnosed after a routine blood or urine test. In later stages, myeloma causes symptoms including: a persistent dull ache or areas of tenderness in your bones, weak bones that fracture easily, tiredness, weakness, shortness of breath, anaemia, repeated infections, kidney problems, bruising and unusual bleeding (for example frequent nose bleeds, bleeding gums and heavy periods).[8]

The exact cause of MM is not known, however it is associated with monoclonal gammopathy of unknown significance (MGUS) which causes an excess of immunoglobulins in the blood. Risk factors for MM include age, gender and ethnicity. The risk of MM increases with age, with most people diagnosed in their mid-60s. Men are more likely to develop the disease than women, and MM is twice as common in black populations compared with white. Other risk factors include having a family history of the disease, having taken immunosuppressants and past exposure to radiation.[8,11]

When diagnosed, MM is staged using the international staging system (ISS) which is based on two blood tests. These tests measure the amount of β2-microglobulin (β2-M), albumin and lactate dehydrogenase (LDH) in the blood. MM is then classified further by levels of calcium and kidney damage markers, anaemia and bone damage, as well as whether the patient is symptomatic or asymptomatic.[12]

Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[13] Relapsed (or recurrent) multiple myeloma is when cancer returns after treatment or after a period of remission.[14] Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016 myeloma was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[16] In England, in 2017, there were 5,034 newly diagnosed cases of multiple myeloma and malignant plasma cell neoplasms (ICD-10: C90). Incidence is strongly linked to

age, with the highest rates in people ages 70 to 89 years.[17] Over the last decade, incidence rates have increased by a seventh (to 15%), represented by an increase in males by 15% and in females by 12%. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[16] A systematic review and economic evaluation carried out in Europe in 2015 found that almost 10% of patients treated were relapsed or refractory to both proteasome inhibitors and immunomodulatory agent based treatment regimens.[18]

In England, in 2018-19, there were 142, 827 finished consultant episodes and 137,870 hospital admissions with a primary diagnosis of MM (ICD-10 code: C90.0), resulting in 89,190 bed days and 126,115 day cases.[19] Almost half (47%) of people diagnosed with myeloma in England and Wales survive their disease for 5 years or more, with a third surviving for 10 years or more.[16] In England in 2017, there were 2,756 registrations of death where MM was recorded as the underlying cause.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Most patients experience serial relapse and will be treated with most available agents at some point during their disease course.[20] 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).[21] 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. [22]

A non-pharmacological treatment option for relapsed or refractory MM is a second autologous stem cell transplant, depending on the response to the first.[23] Patients may also receive medicines and procedures to prevent and treat problems caused by myeloma rather than the condition itself– such as bone pain, fractures and anaemia.[8]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[23]
In instances of first relapse, the guidelines recommend the use of:

- Daratumumab plus bortezomib plus dexamethasone.
- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
- Bortezomib monotherapy – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.

Subsequent relapse treatment may include:[23]

- Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
- Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy.
- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.

- Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immune-modulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

PLACE OF TECHNOLOGY

If licensed, JNJ-68284528 will provide an additional treatment option for relapsed or refractory multiple myeloma.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**CARTITUDE-4** (NCT04181827), EudraCt 2019-001413-16. A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA, Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects With Relapsed and Lenalidomide-Refractory Multiple Myeloma. **Phase III.** **Locations:** Europe (including the UK), USA and others
Trial design	Randomised, parallel assignment, open label trial
Population	- N=400 (planned) - Adults (18 and over) - Relapsed and Lenalidomide-Refractory Multiple Myeloma
Intervention(s)	One or two rounds of bridging therapy + JNJ-68284528 intravenous [IV] infusion 0.5x10^6 CAR-positive viable T-cells/Kg + conditioning regimen (300mg/m^2 IV and 30mg/m^2 fludarabine)
Comparator(s)	Standard therapy (Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd))
Outcome(s)	Progression free survival (PFS)[Time frame: until end of study (up to six years)]. See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**CARTITUDE-2** (NCT04133636), EudraCT (2018-004124-10), A Phase 2, Multi-cohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA in Subjects With Multiple Myeloma. **Phase II** **Locations:** Europe (excluding the UK), USA and Israel
Trial design	Single group assignment, open label trial
Population	- N=80 (planned) - Adults (18 and over) - Multiple myeloma

Intervention(s)	- JNJ-68284528 IV
Comparator(s)	-
Outcome(s)	Percentage of Participants with Negative Minimal Residual Disease (MRD) [Time Frame: At least 1 year after JNJ-68284528 infusion on Day 1]. See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**CARTITUDE-1** (NCT03548207), EudraCT 2018-000121-32, A Phase 1b-2, Open-Label Study of JNJ-68284528, A Chimeric Antigen Receptor T-Cell (CAR-T) Therapy Directed Against BCMA in Subjects With Relapsed or Refractory Multiple Myeloma. **Phase Ib/II** **Locations:** US
Trial design	Single group assignment, open label trial
Population	- N=110 (actual) - Adults (18 and over) - Relapsed or refractory multiple myeloma
Intervention(s)	- JNJ-68284528 as a single infusion
Comparator(s)	- -
Outcome(s)	- Number of Participants with Adverse Events [Time Frame: Minimum 2 years after JNJ-68284528 infusion (Day 1)] - Number of Participants with Adverse Events by Severity [Time Frame: Minimum 2 years after JNJ-68284528 infusion (Day 1)] - Overall Response Rate (ORR) [Time Frame: Minimum 2 years after JNJ-68284528 infusion (Day 1)] - See trial record for full list of outcomes
Results (efficacy)	Results from the Phase 1b portion of the CARTITUDE-1 study showed early and deep responses among patients (n=29) with a median of five prior multiple myeloma treatment regimens (range, 3-18) treated with JNJ-68284528 (median administered dose 0.73x106 CAR+ viable T cells/kg), with 100 percent of patients achieving a response (95 percent confidence interval [CI], 76-95) at a median six-month follow-up. The overall response rate (ORR) included 69 percent of patients achieving a complete response (CR) or better (66 percent achieving a stringent CR); 86 percent of patients achieving a very good partial response (VGPR) or better; and 14 percent of patients achieving a partial response (PR). In addition, 100 percent of evaluable patients achieved early minimal residual disease (MRD)-negative disease status at day 28 post-infusion. At the six-month follow-up, 27 of 29 patients were progression-free. Based on the Phase 1b results, a recommended Phase 2 dose of 0.75x106 CAR+ viable T cells/kg was confirmed.[4]

Results (safety)	The most common adverse events (AEs) observed in the CARTITUDE-1 study were cytokine release syndrome (CRS) (93 percent); neutropenia (93 percent); anaemia (86 percent); and thrombocytopenia (86 percent). In patients who experienced grade 3 and above AEs (25 percent), the most common were neutropenia (93 percent); thrombocytopenia (69 percent); and anaemia (55 percent). A majority of patients (86 percent) experienced grade 1-2 CRS. One patient experienced grade 3 CRS and one patient died of complications from grade 5 CRS at day 99.[4]

Trial	**LEGEND-2** (NCT03090659), A Clinical Study of Legend Biotech BCMA-chimeric Antigen Receptor Technology in Treating Relapsed/Refractory (R/R) Multiple Myeloma Patients. **Phase I/II** **Locations:** China
Trial design	Single group assignment, open label trial
Population	- N=74 (actual) - Adults (18 and over) - Relapsed or refractory multiple myeloma
Intervention(s)	Split doses of LCAR-B38M cells (JNJ-68284528) (total dose of 0.5-5millions/kg cells in 20%, 30% and 50% split) except in one centre where the total dose was administered as a single infusion.
Comparator(s)	-
Outcome(s)	Occurrence of treatment related adverse events as assessed by CTCAE v4.0 [Time Frame: Day 1-30 days after injection] See trial record for full list of outcomes
Results (efficacy)	JNJ-68284528 demonstrated deep and durable responses in patients with R/R MM.[24]
Results (safety)	JNJ-68284528 cell therapy displayed a manageable safety profile.[24]

ESTIMATED COST

The cost of JNJ-68284528 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma (ID1620). Expected date of issue: To be confirmed.
- NICE technology appraisal in development. Selinexor with low-dose dexamethasone for treating refractory multiple myeloma (ID1535). Expected date of issue: January 2021.

- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (ID1477). Expected date of issue: August 2020
- NICE technology appraisal. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (TA586). June 2019.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
- NICE technology appraisal. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). April 2019
- 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. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.
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- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[27]
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ADDITIONAL INFORMATION

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