Health Technology Briefing
April 2022

REGN5458 for relapsed or refractory multiple myeloma

Company/Developer	Regeneron Pharmaceuticals Inc

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27480	NICE ID: 10443	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II/I clinical trials

Summary

REGN5458 is in clinical development for the treatment of adults with multiple myeloma (MM) whose disease has returned following treatment. MM is a form of cancer that occurs in immune cells found in bone marrow. The disease occurs due to uncontrolled duplication of these immune cells, known as plasma cells. Symptoms of MM can include broken bones or bone pain, fatigue, persistent infections, nausea and spinal cord compression. Despite many different therapeutic options being available to people with MM, the disease often returns following treatment.

REGN5458 is a human monoclonal antibody, which is a manufactured version of an immune protein created by the body to fight infection. It is given as an intravenous (IV) infusion. REGN5458 is a bispecific antibody (bsAb), which means that it can attach to two targets simultaneously. This mechanism allows the drug to bring together the plasma cells that are causing disease and immune cells which are able to attack the plasma cells, resulting in anti-tumour activity. This treatment approach is new and there are no therapies using this approach currently recommended for treatment of MM. If licensed, it may be able to offer improved treatment outcomes for people with MM who have failed on previous recommended therapies.

Proposed Indication

Treatment of adults with relapsed or refractory MM.[1]

Technology

Description

REGN5458 is an anti-BCMA x anti-CD3 bispecific antibody with an Fc domain and anti-BCMA/anti-CD3 Fab domains.[2] It binds to both BCMA on plasma cells and to CD3 on T-cells, thereby utilising BCMA to redirect T-cell effector function towards MM cells.[3] This then results in T-cell binding to tumour cells, activation and tumour cell lysis.[2]

REGN5458 is currently in phase I/II clinical development for the treatment of adults with relapsed or refractory MM. In a phase I/II clinical trial (NCT03761108), participants will receive REGN5458 via intravenous (IV) infusion at multiple dose levels ranging from 3-800mg until disease progression or other unspecified discontinuation criterion is met.[1,4]

Key Innovation

Despite many advances in the treatment of MM, there is still an unmet need for treatment of patients who are relapsed/refractory, including those who are double and triple refractory. Treatment with bispecific antibodies such as REGN5458 has shown promise in early clinical trials. These antibodies are designed to target plasma and immune effector cells, which creates an immunologic synapse leading to T-cell activation and destruction of the plasma cells responsible for MM.[5] Additionally, bispecific antibodies directly stimulate CD3 and therefore bypass the need for T-cell receptors. This means that they can activate T-cells independent from major histocompatibility complex (MHC) class I. Bispecific antibodies can also activate T-cells in the absence of co-stimulation. These characteristics make REGN5458 a promising treatment approach for MM.[2] There are currently no bispecific antibodies that have a Marketing Authorisation for MM.

If licenced, REGN5458 will offer a treatment option for adults with relapsed or refractory MM.

Regulatory & Development Status

REGN5458 does not currently have Marketing Authorisation in the UK for any indication.

Patient Group

Disease Area and Clinical Need

MM is a haematological malignancy that occurs due to clonal expansion of malignantly transformed plasma cells located in the bone marrow. These cells are usually responsible for the production of immunoglobulin. MM may affect many areas of the body including bones, kidneys, blood and the immune system.[2,6] Symptoms of MM can include broken bones or bone pain, fatigue, persistent infections, nausea and spinal cord compression.[7] Relapsed MM is a stage of disease where a patient has previously gone into complete or partial remission but then the disease has come back.[8] Refractory MM is a stage of disease where a patient stops responding to treatment.[9]

On average between 2016-2018 in the UK there were 5,951 new cases of MM and 3,085 deaths from MM per year.[10] In 2020-21 in England there were 103,209 hospital admissions and 107,457 finished

consultant episodes for MM (ICD-10 C90.0).[11] Approximately 52% of MM patients will survive for five years following a diagnosis.[12]

Recommended Treatment Options

For relapsed or refractory MM, NICE recommends the following treatment options:[13]

- Carfilzomib with dexamethasone and lenalidomide
- Isatuximab with pomalidomide and dexamethasone
- Carflizomib
- Lenalidomide plus dexamethasone
- Lenalidomide
- Daratumumab with bortezomib and dexamethasone
- Daratumumab
- Ixazomib with lenalidomide and dexamethasone
- Pomalidomide
- Panobinostat
- Bortezomib

Clinical Trial Information

Trial	NCT03761108; 2018-003188-78; Phase 1/2 FIH Study of REGN5458 (Anti-BCMA x Anti-CD3 Bispecific Antibody) in Patients With Relapsed or Refractory Multiple Myeloma **Phase I/II** – recruiting **Location(s):** USA and 2 EU countries **Primary Completion Date:** May 2025
Trial Design	Sequential assignment, open-label
Population	N=~292; aged 18 years and older; diagnosis of active MM; progression on or after at least 3 lines of therapy, or intolerance of therapy, including a proteasome inhibitor, an IMiD and an anti-CD38 antibody; penta-exposed
Intervention(s)	3-800mg REGN5458 IV[4]
Comparator(s)	No comparator
Outcome(s)	• Incidence of dose-limiting toxicities (DLTs) from the first dose through the end of the DLT observation period [Time frame: Up to 28 days] • Incidence and severity of treatment-emergent adverse events (TEAEs) [Time frame: Up to 5 years] • Incidence and severity of adverse events of special interest (AESIs) [Time frame: Up to 5 years] • Objective response rate (ORR) as measured using the International Myeloma Working Group criteria [Time frame: Up to 5 years] See trial record for full list of other outcomes
Results (efficacy)	• Among patients who responded across all dose groups (3-800 mg), there was a 90% probability of being event-free (i.e., alive without disease progression) 8 months from the time of response. 86% (n=32/37)

	achieved a very good partial response (VGPR) or better. 43% (n=16/37) achieved a complete response (CR), with 40% of evaluable CR patients (n=4/10) being minimal residual disease (MRD) negative. • 51% overall response rate (ORR) across all dose groups, rising to 75% in patients who received higher doses of REGN5458 (200-800 mg). • Responses occurred rapidly, usually within the first month of treatment, and continue to deepen with longer treatment; the higher dose groups currently have substantially shorter follow up.[4]
Results (safety)	• The safety profile was generally consistent across all dose levels. Cytokine release syndrome (CRS) was reported in 38% of patients (n=28), the majority of which were Grade 1 (n=25), with no cases ≥Grade 3. The other most common treatment-emergent adverse events (TEAEs) were fatigue (n=33), pyrexia (n=26), nausea (n=24) and anaemia (n=23). The most common ≥Grade 3 TEAEs were anaemia (n=17), neutropenia (n=16), lymphopenia (n=14), thrombocytopenia (n=10) and pneumonia (n=9). There were 5 deaths in the trial, all due to infection; none were considered related to the study medication by investigators.[4]

Estimated Cost

The cost of REGN5458 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies (GID-TA10672). Expected publication date TBC.
- NICE technology appraisal in development. Selinexor with bortezomib and low-dose dexamethasone for treating relapsed refractory multiple myeloma. (GID-TA10646). Expected publication date TBC.
- NICE technology appraisal in development. Teclistamab for treating relapsed or refractory multiple myeloma after 3 therapies. (GID-TA10968). Expected publication date TBC.
- NICE technology appraisal in development. Talquetamab for treating relapsed or refractory multiple myeloma after 3 therapies. (GID-TA10969). Expected publication date TBC.
- NICE technology appraisal in development. Ciltacabtagene autoleucel for treating relapsed and lenalidomide-refractory multiple myeloma after 1 to 3 therapies. (GID-TA10905). Expected publication date TBC.
- NICE technology appraisal in development. Ciltacabtagene autoleucel for treating relapsed or refractory multiple myeloma. (GID-TA10806). Expected publication date TBC.
- NICE technology appraisal in development. Venetoclax with dexamethasone for treating relapsed or refractory t(11;14)-positive multiple myeloma after lenalidomide and a proteasome inhibitor. (GID-TA10926). Expected publication date TBC.
- NICE technology appraisal in development. Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies. (GID-TA10353). Expected publication date TBC.

- NICE technology appraisal in development. Elranatamab for treating refractory multiple myeloma after 3 standard therapies (GID-TA10918). Expected publication date TBC.
- NICE technology appraisal in development. Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies (GID-TA10568). Expected publication date TBC.
- NICE technology appraisal in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma. (GID-TA10579). Expected publication date: October 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. 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). Last updated: 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. 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 technology appraisal. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma. (GID-TA10744). Suspended.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. 2015. B04/P/a.
- 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. 2013/14. NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

Other Guidance

- Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. 2021.[14]

- Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[15]

Additional Information

Regeneron Pharmaceuticals did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *First in Human (FIH) Study of REGN5458 in Patients With Relapsed or Refractory Multiple Myeloma*. *Trial ID: NCT03761108*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03761108 [Accessed 23 February 2022].

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7 Cancer Research UK. *Symptoms of myeloma.* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/symptoms [Accessed 22 March 2022].

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9 Blood Cancer UK. *Myeloma relapsed and refractory treatment.* Available from: https://bloodcancer.org.uk/understanding-blood-cancer/myeloma/myeloma-treatment-side-effects/relapsed-refractory-myeloma/ [Accessed 30 March 2022].

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.