Health Technology Briefing
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Daratumumab for the treating high-risk smouldering multiple myeloma

Company/Developer	Janssen-Cilag Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 20561	NICE TSID: 10402	UKPS ID: 648547

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Daratumumab is in clinical development for high-risk smouldering multiple myeloma (SMM). SMM is an early form of myeloma which usually progresses to active myeloma, but at a slow rate. SMM is a precancerous condition that changes certain proteins in blood and/or increases plasma cells in the bone marrow but does not cause symptoms of disease. SSM is often diagnosed by chance, following a routine health check or blood tests for another condition. Within 5 years, about half of those diagnosed with the condition will develop multiple myeloma (MM). 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.

Daratumumab is a type of immune therapy that acts by inhibiting the growth of cancer cells in MM via a surface protein called CD38. It is administered under the skin, and by attaching to CD38 on these cells, daratumumab activates the immune system to kill the abnormal white blood cells. Daratumumab will offer a novel treatment option for patients with high-risk SMM.

Proposed Indication

For the treatment of patients with high-risk smouldering multiple myeloma (SMM).[1]

Technology

Description

Daratumumab is an immunoglobin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma (MM) tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity. Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumour cells. Based on in vitro studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody- dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.[2]

Daratumumab is currently in clinical development for the treatment of high-risk SMM. In the phase III trial (NCT03301220), daratumumab 1800mg is administered subcutaneously (SC) once weekly in cycle 1 and 2, every 2 weeks for cycles 3 to 6, and subsequently every 4 weeks until 39 cycles or up to 36 months or until confirmed disease progression, unacceptable toxicity or withdrawal from the study treatment, study termination or study completion.[1]

Key Innovation

Currently, SMM patients do not receive any treatment until progression to symptomatic MM. This 'watch and wait' approach is based on clinical trials in which early treatment intervention was not associated with survival benefit.[3] Current guidelines for SMM recommend active monitoring until the onset of MM before initiating treatment or enrolment in a clinical trial.[4] A recent clinical trial studying Lenalidomide-dexamethasone versus standard observation has shown evidence of the positive effect of early intervention on overall survival and time to disease progression.[5] Earlier intervention using daratumumab may delay progression to MM.[6]

Regulatory & Development Status

Daratumumab currently has Marketing Authorisation in the EU/UK for multiple myeloma and Primary amyloidosis (AL amyloidosis).[7]

Daratumumab is currently in phase II and III clinical trials for several indications including the following:[8,9]

- Waldenstrom's disease
- Plasma cell myeloma
- Relapsed or refractory T-Cell lymphoma

Patient Group

Disease Area and Clinical Need

SMM is an asymptomatic plasma cell dyscrasia with a high propensity to progress to symptomatic MM. It meets all the diagnostic criteria for MM, but without lytic bone disease, anaemia, renal failure, or hypercalcemia (CRAB symptoms).[3] SMM is a heterogeneous disorder including patients with varying rates of progression to symptomatic melanoma, with some patients progressing quickly, whereas others remaining clinically stable several years after diagnosis.[10] 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.[11,12] Risk factors for MM include age, gender and ethnicity.[13] Other risk factors include having a family history of the disease, having taken immunosuppressants and past exposure to radiation.[14] MM patients often have pronounced symptoms and substantially reduced health-related quality of life. Around 80% of patients experience skeletal destruction, approximately 73% will have anaemia at diagnosis and about 30% of patients present with renal insufficiency.[15]

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.[16] 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).[17] 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.[18] No SMM population estimates for the UK could be found in current published literature.

Recommended Treatment Options

Currently, SMM is not generally treated until active myeloma develops. This is because, for the majority of patients, the benefit of treatment is outweighed by its risks due to potential side-effects.[19]

Clinical Trial Information

Trial	NCT03301220, EudraCT 2016-001205-16; A Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects With High-Risk Smouldering Multiple Myeloma **Phase III –** Active, not recruiting **Location(s):** 12 EU countries, UK, USA, Canada and other countries **Primary Completion date:** April 2023
Trial Design	Randomised, open label, parallel assignment
Population	N= 390 (actual); subjects aged 18 years and older with high-risk SMM
Intervention(s)	Participants will receive 1800mg of daratumumab by SC injection once weekly for cycle 1 and 2, every 2 weeks for cycle 3 to 6, and subsequently every 4 weeks until 39 cycles or up to 36 months or until confirmed disease progression, unacceptable toxicity or withdrawal from the study treatment, study termination or study completion.

Comparator(s)	Active monitoring
Outcome(s)	Progression-free Survival (PFS) [Time frame: From the date of randomisation to active MM or the date of death, whichever occurs first (up to approximately 8 years)] See trial records for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Daratumumab is already marketed in the UK; a vial for injection (1800mg/15mL) costs £4,320, a vial for infusion costs either £360 (100mg/5mL) or £1,440 (400mg/20mL).[20]

Relevant Guidance

NICE Guidance

- 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: Haematopoietic Stem Cell Transplantation (HSCT) (All ages): Revised. 2015. B04/P/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B/15/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

- 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:
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Additional Information

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