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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Daratumumab in addition to cyclophosphamide, bortezomib and dexamethasone for newly diagnosed systemic amyloid light-chain amyloidosis

NIHRIO ID	21696	**NICE ID**	10272
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	648225

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Daratumumab in addition to cyclophosphamide, bortezomib and dexamethasone (CyBorD) is in clinical development for newly diagnosed systemic amyloid light-chain (AL) amyloidosis in adults. AL amyloidosis belongs to a group of diseases called systemic amyloidosis in which deposits of proteins (called amyloids) accumulate and cause damage in tissues and organs such as the kidneys, liver, gut, heart and nerves. In AL amyloidosis, the deposits are made up of proteins (called immunoglobulin light chains) produced in excess by malfunctioning white blood cells in the bone marrow.

Daratumumab is a monoclonal antibody (a type of protein) designed to recognise and attach to a specific structure called 'CD38' which is found in great numbers on the white blood cells that produce immunoglobulin light chains. Once attached, it is expected to activate the immune system to attack and kill the white blood cells. This is expected to reduce the deposits of proteins, and so improve symptoms of the disease. If licensed, daratumumab in addition to CyBorD will offer an additional treatment option for newly diagnosed systemic AL amyloidosis in adults.

PROPOSED INDICATION

Treatment of newly diagnosed systemic amyloid light-chain amyloidosis in adults.[a]

TECHNOLOGY

DESCRIPTION

Daratumumab (Darzalex) is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma 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.[1]

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+T_{regs}) and B cells (CD38+B_{regs}) 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.[1]

Daratumumab in addition to cyclophosphamide, bortezomib and dexamethasone (CyBorD) is currently in clinical development for the treatment of newly diagnosed systemic amyloid light-chain amyloidosis in adults. In the phase III clinical trial (NCT03201965), participants will receive dexamethasone (20 mg orally or intravenous (IV) dose as premedication and 20 mg on the day after daratumumab dosing) followed by 1,800 mg of daratumumab subcutaneously followed by cyclophosphamide (300 mg/m^2 orally or IV dose weekly) and bortezomib (1.3 mg/m^2 subcutaneous injection weekly) on Days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles. Daratumumab will be administered weekly for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (cycles 3-6), and then every 4 weeks until progression of disease or subsequent therapy for a maximum of 2 years.[2]

INNOVATION AND/OR ADVANTAGES

Autologous stem cell transplantation (ASCT) has been used as treatment for immunoglobulin amyloid light-chain (AL) amyloidosis for over two decades with improving outcomes; however, the majority of patients are not candidates for this therapy at diagnosis. Novel agents such as immunomodulatory drugs, proteasome inhibitors, and immunotherapy with monoclonal antibodies targeting CD38 have been adopted from the multiple myeloma spheres with encouraging results.[3]

The current therapeutic approach for AL amyloidosis is to target the toxic amyloidogenic light chain-producing plasma cells. Achieving a reduction in the involved free light chains (i.e., a haematological response) is considered a critical endpoint as it is crucial to prevent further

[a] Information provided by Janssen in UK PharmaScan

organ damage. The clonal plasma cells in AL express CD38, making daratumumab a potentially active treatment.[4]

In previous studies of daratumumab monotherapy in pre-treated AL amyloidosis patients, the overall haematological response rate was 86% in the 15 patients assessable for haematological response. Five patients (33%) achieved a complete response and eight patients (53%) attained a very good partial response.[4] The most common adverse event was infusion reactions. The subcutaneous administration of daratumumab is expected to contribute to the safety of these patients that often have some degree of cardiac compromise.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Daratumumab (subcutaneous administration) does not currently have Marketing Authorisation in the EU/UK for any indication.

Daratumumab (concentrate for solution for infusion) is indicated:[1]

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

The very common adverse events (≥ 20%) reported among patients receiving daratumumab were: pneumonia, bronchitis, upper respiratory tract infection, neutropenia, thrombocytopenia, anaemia, lymphopenia, leukopenia, decreased appetite, peripheral sensory neuropathy, headache, hypertension, cough, dyspnoea, diarrhoea, constipation, nausea, vomiting, back pain, muscle spasms, fatigue, oedema peripheral, pyrexia, asthenia, and infusion-related reaction.[1]

Daratumumab is currently in phase II and phase III development for the treatment of various conditions such as myeloma multiple, lymphoma, smoldering multiple myeloma, myelodysplastic syndromes, non-small-cell lung cancer, Waldenström macroglobulinemia, relapsed or refractory chronic lymphocytic leukaemia, Alzheimer disease, non-Hodgkin's lymphoma, and Hodgkin Lymphoma.[6]

Daratumumab received European Orphan Designation for the treatment of AL amyloidosis in May 2018.[7]

PATIENT GROUP

DISEASE BACKGROUND

Amyloidosis is the name for a group of rare, serious conditions caused by a build-up of an abnormal protein called amyloid in organs and tissues throughout the body. The build-up of amyloid proteins (deposits) can make it difficult for the organs and tissues to work properly. Without treatment, this can lead to organ failure. AL amyloidosis (previously known as primary amyloidosis), is the most common type.[8]

The symptoms of AL amyloidosis depend on which tissues and organs are affected. Most people with AL amyloidosis have a build-up of amyloid proteins (amyloid deposits) in their kidneys, and are at risk of kidney failure. Symptoms of kidney failure include swelling, often in the legs, caused by fluid retention (oedema), tiredness, weakness, and loss of appetite. Deposits of amyloid in the heart can cause the muscles to become stiffer, making it more difficult to pump blood around the body. This may result in heart failure, which can cause symptoms such as shortness of breath, oedema, an abnormal heartbeat (arrhythmia). Amyloid proteins can also build up in other organs and tissues, like the liver, spleen, nerves or digestive system. This means people may have any of the following symptoms: feeling lightheaded or fainting, particularly after standing or sitting up, numbness or a tingling feeling in the hands and feet (peripheral neuropathy), nausea, diarrhoea or constipation, numbness, tingling and pain in the wrist, hand and fingers (carpal tunnel syndrome), an enlarged tongue. AL amyloidosis does not affect the brain, so it does not cause any problems with memory or thinking.[8]

AL amyloidosis is caused by an abnormality in plasma cells that lead to the production of abnormal forms of light chain proteins, which enter the bloodstream and can form amyloid deposits. Healthy people have normal light chain proteins in their blood that are part of their natural antibody proteins, which help protect the body from illness and infection. The abnormal light chains in patients with AL amyloidosis clump together into thread-like strings (amyloid fibrils) that the body cannot clear away easily. Over time, amyloid fibrils build up as AL amyloid deposits in tissues and organs. This gradually stops them functioning properly, causing the many symptoms of AL amyloidosis. Unlike some other types of amyloidosis, AL amyloidosis is not inherited, so a person with the condition cannot pass it on to their children.[8]

CLINICAL NEED AND BURDEN OF DISEASE

AL amyloidosis is a relatively rare condition, with approximately 500 – 600 people diagnosed in the UK each year.[9]

According to the report performed by the Orphanet Report Series in January 2019, the prevalence estimated in Europe for AL amyloidosis was 11.0 per 100,000 people.[10] Applying this estimate to the 2018 mid-year population estimates for England and Wales, this would equate to approximately 6,503 cases of AL amyloidosis.[11]

In England, in 2018-2019, there were 4,221 finished consultant episodes (FCE) for amyloidosis (ICD 10: E85), resulting in 3,527 hospital admissions (of which 2,695 were day cases) and 8,265 FCE bed days.[12]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

AL amyloidosis is currently incurable. Treatment options aim to control the condition, reducing symptoms and improving quality of life by destroying the abnormal plasma cells that produce the amyloid protein. This can help to prevent new deposits forming.[13]

Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes with the treatment goal to achieve a very good partial response if possible.[14]

Localized AL amyloidosis does occur rarely and, if problematic, can usually be treated by local resection or, in selected cases, radiotherapy.[14]

Where myeloma and AL amyloidosis co-exist, choice of treatment for myeloma should take into account the extent of organ involvement with amyloid and the potential toxicities of individual treatments.[14]

CURRENT TREATMENT OPTIONS

First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminaemia, fluid retention).[14]

Bortezomib is preferably given subcutaneously to reduce toxicity but may be given intravenously in patients with severe fluid overload where there is a concern about adequacy of absorption.[14]

Thalidomide in combination with cyclophosphamide and dexamethasone is effective in the treatment of AL amyloidosis.[14]

Thalidomide should be used with caution in patients with cardiac stage III disease and those with grade III–IV neuropathy. In patients with grade III–IV neuropathy strong consideration must be given to avoiding neurotoxic drugs (thalidomide and bortezomib).[14]

High dose melphalan (HDM) and autologous stem cell transplantation (ASCT) (HDM-ASCT) is the preferred first line treatment for selected patients up to 65–70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in the bone marrow at the time of transplant and lacking the contraindications mentioned in the next point.[14]

HDM-ASCT is not generally recommended as first line therapy for patients with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide (NT-proBNP) >590 pmol/l and/or troponin-T > 0·06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, advanced renal failure, age over 70 years, symptomatic recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status (>2).[14]

PLACE OF TECHNOLOGY

If licensed, daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) will offer an additional treatment option for newly diagnosed systemic AL amyloidosis in adults.

CLINICAL TRIAL INFORMATION

Trial	NCT03201965, CR108193, EudraCT 2016-001737-27; A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination With Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared to CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis **Phase III** **Location(s):** EU countries (including the UK), Canada, USA, and other countries
Trial design	Randomised, active-controlled, open label
Population	N=417; aged 18 years and older; histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarizing light microscopy of green bi-refringent material in congo red stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance; measurable disease of AL amyloidosis as defined by at least one of the following: (1) serum monoclonal (M)-protein greater than or equal (>=) 0.5 grams/deciliter (g/dL) by protein electrophoresis (routine serum protein electrophoresis and immunofixation [IFE] performed at a central laboratory); (2) serum free light chain greater than or equal to (>=) 50 milligram/Liter (mg/L) with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) >= 50 mg/L; one or more organs impacted by AL amyloidosis according to consensus guidelines; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2.
Intervention(s)	Dexamethasone (20 mg orally or IV dose as premedication and 20 mg on the day after daratumumab dosing) followed by 1800 mg of daratumumab subcutaneously followed by cyclophosphamide (300 mg/m^2 orally or IV dose weekly) and bortezomib (1.3 mg/m^2 subcutaneous injection weekly) on Days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles. Daratumumab will be administered weekly for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (cycles 3-6), and then every 4 weeks until progression of disease or subsequent therapy for a maximum of 2 years.
Comparator(s)	Dexamethasone (40 milligrams [mg] orally or intravenous [IV] dose), followed by cyclophosphamide (300 milligram per meter square [mg/m^2] orally or IV dose), then bortezomib (1.3 mg/m^2 subcutaneous injection) weekly on Days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles.
Outcome(s)	Percentage of participants with overall complete hematologic response [Time frame: approximately 3 years]
Key Results	-
Adverse effects (AEs)	-

ESTIMATED COST

The cost of daratumumab (subcutaneous) is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidelines. Myeloma: diagnosis and management (NG35). February 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

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ADDITIONAL INFORMATION

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