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HEALTH TECHNOLOGY BRIEFING
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Polatuzumab vedotin in addition to R-CHP for diffuse large B-cell lymphoma – first line

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Developer/Company	Roche Products Ltd	**UKPS ID**	656162

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Polatuzumab vedotin in combination with rituximab and cyclophosphamide, doxorubicin, prednisone/prednisolone (R-CHP) chemotherapy is in clinical development for patients with diffuse large B-cell lymphoma (DLBCL) that has been untreated. DLBCL is a cancer affecting a type of white blood cells called lymphocytes or B-cells. DLBCL is an aggressive cancer and although it can be cured in more than half of people affected, it remains a serious and life-threatening disease, particularly when it relapses or does not respond to treatment.

Polatuzumab vedotin is a first-in-class drug specifically developed for the treatment of cancers that affect the blood and lymph system. It is an antibody that binds to CD79b, which is a protein on the surface of cancerous B-cells. It is administered as an intravenous infusion, absorbed by the cancer cells and the chemotherapy agent linked to the antibody releases inside the cancer cells, stops them from dividing and kills them. If licenced polatuzumab vedotin in addition to R-CHP would offer an additional treatment option for patients with untreated DLBCL.

PROPOSED INDICATION

Polatuzumab vedotin in combination with R-CHP chemotherapy for the treatment of patients with previously untreated DLBCL.[a]

TECHNOLOGY

DESCRIPTION

Polatuzumab vedotin (DCDS4501A, RG7596, Polivy) is a first-in-class anti-CD79b antibody drug conjugate (ADC).[1] It is made up of a monoclonal antibody combined with a cytotoxic (cell-killing) agent called monomethyl auristatin E (MMAE). CD79b is a cell surface antigen expressed on the surface of normal and malignant B-cells, and the anti-CD79b monoclonal antibody is designed to attach specifically to CD79b expressed on the malignant B-cells. When the antibody attaches to CD79b, the B-cells rapidly internalise the medicine and MMAE is released inside them. MMAE stops microtubules in the B-cells from working. Microtubules are structures that cells need to survive and divide. By targeting the malignant B cells and causing them to die, the medicine is expected to reduce symptoms of the disease.[2-4] The CD79b protein is highly specific and expressed in the majority of types of B-cell Non-Hodgkin Lymphoma (NHL), making it a promising target for the development of new therapies.[5]

Polatuzumab vedotin in combination with R-CHP chemotherapy is in clinical development for patients with previously untreated DLBCL. In the phase III clinical trial (NCT03274492) polatuzumab vedotin was administered intravenously (IV) at 1.8 milligrams per kilogram (mg/kg), placebo for vincristine IV, rituximab 375 milligrams per square meter (mg/m^2) IV, cyclophosphamide 750 mg/m^2 IV, and doxorubicin 50 mg/m^2 IV on Day 1 and prednisone 100 milligrams per day (mg/day) orally on Days 1-5 of every 21-day cycle, for 6 cycles. Rituximab 375 mg/m^2 IV was administered as monotherapy in Cycles 7 and 8.[6]

INNOVATION AND/OR ADVANTAGES

Antibody-drug conjugates (ADCs) are an innovative class of anti-cancer treatment that comprise a monoclonal antibody targeted to a tumour antigen, a chemical linker, and a potent cytotoxic agent, which is often too toxic to be given as conventional chemotherapy.[7,8] Polatuzumab vedotin is the first ADC targeting CD79b, a signalling component of the B cell receptor expressed on the surface of B cells that is found in abundance in people with DLBCL.

Polatuzumab vedotin restricts CD79b expression in malignant cells, is rapidly internalised into the cells and enables intracellular delivery of a potent anti-mitotic agent (MMAE). MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.[8-10]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

[a] Information provided by Roche Products Ltd on UK PharmaScan

Polatuzumab vedotin, in combination with rituximab and bendamustine, is currently licenced in the EU/UK for relapsed or refractory DLBCL in adults who cannot have a haemopoietic stem cell transplant.[11] Very common adverse side effects (affecting more than 1 in 10 patients) are fever or chills, diarrhoea or constipation, nausea, vomiting, cough, pneumonia, infusion-related reactions, anaemia, abdominal pain, itchiness, loss of appetite, loss of weight, common cold, herpes infection, dizziness and unusual sensations.[10]

Polatuzumab vedotin has the following regulatory designations/awards:

- An Orphan Drug in the EU in 2018 for the treatment of DLBCL[12]
- A PRIME status for relapsed or refractory DLBCL by the EMA in June 2017[13]
- A Breakthrough Therapy by the US FDA for relapsed or refractory DLBCL in June 2019[14]

Polatuzumab vedotin, in combination with other treatments, is currently in Phase II clinical trials for Hodgkin lymphoma and other non-Hodgkin lymphomas, including triple-hit, double-hit, Richter syndrome, Burkitt, mantle cell and marginal zone.[15]

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer of the lymphatic system.[16] The lymphatic system is a system of thin tubes (lymph vessels) and lymph nodes that run throughout the body. Clear fluid called lymph flows through the lymph vessels and contains infection-fighting white blood cells known as lymphocytes. The lymphatic system is an important part of our immune system as it plays a role in fighting bacteria and other infections and destroying old or abnormal cells, such as cancer cells.[17] Lymphomas are categorised into two broad groups: non-Hodgkin (NHL) and Hodgkin, NHL can be further divided into over 30 different subtypes.[18,19] Around 40% of NHL cases are DLBCL which is a fast growing (high grade) lymphoma subtype that develops when the body makes abnormal B lymphocytes which build up in lymph nodes or other body organs.[20,21] These abnormal cells are spread out (diffuse) rather than grouped together when they are examined under a microscope.[21] The affected lymphocytes start to divide before they are fully mature and lose their infection-fighting properties which makes the body more vulnerable to infection.[22,23]

Because the lymphatic system runs throughout the whole body, NHL can occur anywhere.[23] Often the first symptom of DLBCL is a painless swelling in the neck, armpit, or groin due to enlarged lymph nodes. Sometimes other parts of the body outside the lymph nodes can also be affected such as the stomach, bowel, liver, testis, skin, brain, or eye. Some people with DLBCL may have other more general symptoms which include night sweats, unintentional weight loss, or high temperature.[24,25]

NHL, including DLBCL, are caused by a mutation in the DNA of lymphocytes resulting in them multiplying and growing uncontrollably, but the exact reason why this happens is not known. However, it is more slightly likely to affect men than women and more common in older people.[22,23] A person's risk of developing the disease is increased if they have a medical condition that weakens the immune system, they take immunosuppressant medication or if they have previously been exposed to a common virus called Epstein-Barr virus, which causes

glandular fever. There is also a slightly increased risk of developing NHL if a first degree relative has the condition.[26]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017 12,065 people had NHL, and around 5,500 people are diagnosed with DLBCL each year in the UK.[21,27] In England 2019-20 there were 39,515 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) with 35,369 hospital admissions, 27,422 day cases and 86,774 FCE bed days.[28]

In England and Wales in 2017, 4,348 people died with NHL as underlying cause of death. Based on the fact DLBCL makes up approximately 40% of all NHL cases that is around 1,740 people who died because of DLBCL.[20,29]

Based on cancer stages 1 and 2 where the tumour is relatively small and localised, but may have spread to nearby lymph nodes, patients with DLBCL have a 65-70% survival rate of five years or more. For patients with DLBCL stages 3 and 4, where the cancer is larger and/or spreading to other areas of the body, around 50% will survive for five years or more.[30,31] These survival rates are based on one area of England, for people diagnosed between 2004 and 2011, as there are no UK-wide survival statistics for different types and stages of NHL.[31]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Aims of treatment for DLBL can be the following:

- Cure the lymphoma
- Control the lymphoma for as long as possible
- Manage symptoms
- Stop the lymphoma from spreading to other areas of the body
- Prevent the lymphoma from returning

These can be dependent on the stage of the lymphoma, the patient's symptoms and general health, levels of chemicals in their blood, and whether the lymphoma is likely to come back after treatment.[32]

DLBCL is an aggressive cancer that needs immediate treatment. The aim of treatment in most patients is complete remission and cure.[33] A combination of chemotherapy and the monoclonal antibody rituximab, with or without radiation therapy, can lead to disease remission in a large number of patients with this form of lymphoma (about 60%).[34-36]

CURRENT TREATMENT OPTIONS

In the UK, the most widely used treatment for front-line DLBCL presently is the combination known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). The R-CHOP regimen is usually given in 21-day cycles (once every 21 days) for an average of

6 cycles. However, the length and number of cycles given can vary based on the patient's individual disease and health status. In certain cases 14-day cycles may be used, and for limited stage disease (Stage 2 or 3) 3-4 cycles may be used followed by radiation therapy.[36] Steroids can also be given to enhance the effect of the chemotherapy.[35]

PLACE OF TECHNOLOGY

If licenced polatuzumab vedotin in addition to rituximab and cyclophosphamide, doxorubicin, prednisone/prednisolone (R-CHP) chemotherapy would offer an additional treatment option for patients with untreated DLBCL.

CLINICAL TRIAL INFORMATION

Trial	**POLARIX; NCT03274492; 2017-002023-21;** A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination With Rituximab and CHP (R-CHP) Versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients With Diffuse Large B-Cell Lymphoma **Phase III –** Closed to recruitment, ongoing. **Location(s):** EU (inc UK), US, Canada, and other countries **Primary completion date:** January 2021
Trial design	Randomised, quadruple masked, parallel assignment.
Population	N = 875 (planned), age 18 to 80 years, previously untreated participants with cluster of differentiation 20 (CD20)-positive DLBCL.
Intervention(s)	R-CHP plus vincristine placebo and polatuzumab vedotin every 21-day cycle, for 6 cycles. Polatuzumab vedotin administered intravenously (IV) at 1.8 mg per kg.
Comparator(s)	Matched placebo.
Outcome(s)	Progression-Free Survival (PFS) as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma [Time Frame: From randomization to the first occurrence of disease progression or relapse, or death from any cause, whichever occurs earlier (up to 38 months)]. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of polatuzumab vedotin 140mg powder for concentrate for solution for infusion vials is £11,060 (NHS indicative price, hospital only).[37]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016
- NICE Quality Standard. Haematological cancers (QS150). June 2017

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

OTHER GUIDANCE

- The British Committee for Standards in Haematology. Guidelines for the management of diffuse large B-cell lymphoma. 2016[38]
- The European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2015[39]

ADDITIONAL INFORMATION

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