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HEALTH TECHNOLOGY BRIEFING MARCH 2020

Tafasitamab in combination with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma

NIHRIO ID	10678	**NICE ID**	9671
Developer/Company	Incyte Corp MorphoSys AG	**UKPS ID**	Not Available

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

SUMMARY

Tafasitamab in combination with lenalidomide is currently in clinical development for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). DLBCL is a type of blood cancer that develops when white blood cells, called lymphocytes, grow out of control. The affected lymphocytes lose their infection-fighting ability making the body more susceptible to infection. The first symptom of DLBCL is often a painful swelling in the neck, armpit or groin but there may be other more general symptoms such as night sweats, unintentional weight loss or high temperature. Relapsed cancer refers to cancer that initially responded to treatment but then returned. Refractory cancer refers to cancer that did not respond to treatment.

Tafasitamab is administered by intravenous infusion and works by blocking the protein CD19 which is widely found on the surface of B-cells (a type of lymphocytes). CD19 is considered important for B-cell signalling and therefore blocking this protein induces death in the cancerous B-cells. Lenalidomide works by altering the activity of the body's immune system in order to attack abnormal cells. If licenced, tafasitamab

in combination with lenalidomide will offer an additional treatment option for patients with relapsed or refractory DLBCL.

PROPOSED INDICATION

Tafasitamab in combination with lenalidomide followed by tafasitamab monotherapy as a treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) including DLBCL arising from low-grade lymphoma, and who are not eligible for, or refuse autologous stem cell transplant (ASCT).[1,a]

TECHNOLOGY

DESCRIPTION

Tafasitamab (MOR208) is an investigational humanised Fc-engineered monoclonal antibody directed against CD19. Fc-modification of tafasitamab, which consists of two amino acid substitutions S239D and I332E, is intended to lead to a significant potentiation of antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), thus aiming to improve a key mechanism of tumour cell killing. Tafasitamab has been observed in preclinical models to induce direct apoptosis by binding to CD19.[2,3] The antigen CD19 is broadly expressed on the surface of B-cells and has been reported to enhance B-cell receptor signalling which is assumed to be important for B-cell survival. Therefore, it is considered as a potential target for the treatment of B-cell malignancies such as non-Hodgkin's lymphoma, including DLBCL.[2,4]

Lenalidomide inhibits proliferation, enhances apoptosis, and prohibits the growth of blood vessels (angiogenesis) within certain haematopoietic tumour cells and enhances T-cell and Natural Killer (NK) cell-mediated immunity.[5,6] Lenalidomide works by binding directly to cereblon, which in haematopoietic cells recruits substrate proteins, Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of micro-vessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells and inhibits production of pro-inflammatory cytokines (eg TNF-α and IL-6) by monocytes.[6]

Tafasitamab in combination with lenalidomide is currently in clinical development for the treatment of relapsed or refractory DLBCL. In the phase II clinical trial (NCT02399085; L-MIND) patients are given 12mg/kg tafasitamab by intravenous administration weekly (cycle 1-3) to bi-weekly (cycle 4 onwards) in 4 week cycles in addition to 25mg Lenalidomide by intravenous administration which is given 3 of the 4 weeks for up to 12 weeks. [1]

INNOVATION AND/OR ADVANTAGES

Despite the success of rituximab, resistance occurs in about half of the patients, resulting in non-response to treatment or early relapse with the original disease.[7] Fc-engineering enhances binding of the Fc domain on tafasitamab to activating Fcγ-receptors which has been

[a] Information provided by MorphoSys AG

shown to enhance cytotoxicity, relative to a native non-engineered anti-CD19 antibody in vitro.[3]

Preclinical in vitro and in vivo data have demonstrated increased combinatorial anti-tumour effects with tafasitamab in combination with the immunomodulatory agent lenalidomide. In the phase II study L-MIND (NCT02399085) patients achieved an ORR of 60%, a complete response rate of 42.5% and a median progression-free survival of 12.1 months.[8,9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tafasitamab does not currently have Marketing Authorisation in the EU/UK for any indication.

Tafasitamab is currently in phase II and III development to treat other subtypes of NHL and leukaemia.[10,11]

In December 2014, tafasitamab received an orphan drug designation by the EMA for the treatment of DLBCL.[12,13]

Lenalidomide currently has Marketing Authorisation in the EU/UK for the following indications:[6]

- Multiple myeloma
  As monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation

  As combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

  As combination therapy with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

- Myelodysplastic syndromes
  As monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to low or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion of 5q cytogenic abnormality when other therapeutic options are insufficient or inadequate.

- Mantle cell lymphoma
  As monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma

- Follicular lymphoma
  In combination therapy with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 -3a).

The most common side effects of lenalidomide are relative to the condition for which it is used as a treatment, however common to all different approved indications is neutropenia, diarrhoea, constipation, nausea, tiredness and rash.[5]

In 2017, tafasitamab, in combination with lenalidomide, received a Breakthrough Therapy Designation for relapsed/refractory DLBCL by the FDA.[14]

In May 2011 lenalidomide was granted an orphan drug designation by the EMA for the treatment of DLBCL.[15]

Lenalidomide is currently in phase III development for the treatment of:[16]

- myeloma
- leukaemia
- lymphoma
- anaemia
- myelodysplastic syndromes
- prostate cancer
- plasmacytoma
- radiculopathy
- melanoma
- amyloidosis

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is a cancer of the lymphatic system.[17] The lymphatic system is a system of thin tubes (lymph vessels) and lymph nodes that run throughout the body.[18] Clear fluid called lymph flows through the lymph vessels and contains infection-fighting white blood cells known as lymphocytes.[19] 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.[18] Lymphomas are categorised into two broad groups: non-Hodgkin (NHL) and Hodgkin, NHL can be further divided into over 30 different subtypes.[20,21] 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. These abnormal cells are spread out (diffuse) rather than grouped together when they are examined under a microscope.[22,23] 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.[19,24] Refractory NHL is when the disease has not responded to initial treatment and is getting worse or staying the same. Relapsed NHL is when the NHL initially responded to treatment but then returned.[25]

The lymphatic system runs throughout the entire body and therefore NHL can appear anywhere.[24] The first symptom of DLBCL is often 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. Symptoms are directly related to the amount of pressure the lymphoma is putting on the particular body part affected.[23] Some people with DLBCL may have other more general symptoms which include night sweats, unintentional weight loss or high temperature.[22]

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. 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.[26,27]

CLINICAL NEED AND BURDEN OF DISEASE

NHL is the 6th most common cancer in the UK, accounting for 4% of all new cancer cases. The European age-standardised incidence rate in England in 2017, was 23.2 cases per 100,000.[28,29] Also in England, in 2017, there were 12,065 newly diagnosed cases of NHL (ICD-10 code C82-C85) of which 4,816 were DLBCL (ICD-10 code C83.3).[30]

For the England and Wales deaths registered in 2017, there were 1,105 deaths where diffuse NHL (ICD-10 code C83) was recorded as the underlying cause.[31] The age standardised rates per 100,00 population of registered deaths from diffuse NHL (ICD-code C83) was 2.8 for males and 1.6 for females.[30]

According to the 2018-19 Hospital Episodes Statistics data, there were 37,781 finished consultant episodes (FCE) for DLBCL (ICD-10 code C83.3) that resulted in 33,781 admissions and 83,314 FCE bed days.[32]

In England, between 2013 and 2017 a total of 56,350 NHL patients followed up to 2018, the age standardised one year and five year survival rate was 79.4% and 65.6% respectively.[33]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

At any stage, DLBCL is usually treated with the aim of curing it. It often responds well to treatment and many people go into complete remission. Treatment will depend on the stage of lymphoma the patient has as well as age, general health and fitness and the patient's feelings towards treatment.[23] Since DLBCL can advance quickly, it usually requires immediate treatment. A combination of chemotherapy and immunotherapy, with or without radiation therapy can lead to disease remission in a large number of patients with this form of lymphoma.[34]

About 2/3 of patients can be cured with this 1st line treatment approach. However, the prognosis for patients not responding (refractory patients) or responding for a limited time only (relapsed patients), is dismal as only about 10% of these patients can be cured afterwards by high dose chemotherapy and stem cell transplantation. However, most relapsed / refractory patients are not eligible for this intense treatment approach.[35]

Most people with relapsed or refractory lymphoma are offered further chemo-immunotherapy, known as salvage treatment. The aim of salvage treatment is to reduce the lymphoma as much as possible rather than provide curative or overall survival benefit. In those patients who are fit enough after salvage treatment a stem cell transplant may increase the chance of having long-lasting remission.[23,36,37]

CURRENT TREATMENT OPTIONS

The most commonly used salvage treatment regimens for relapsed or refractory DLBCL include:[23,38]

- R-GDP – rituximab with gemcitabine, dexamethasone and cisplatin
- R-DHAP – rituximab with dexamethasone, high-dose cytarabine and cisplatin
- R-ICE – rituximab with ifosfamide, carboplatin and etoposide

For adults whose DLBCL is relapsed or refractory after 2 or more systemic therapies NICE recommends:[39]

- Tisagenlecleucel
- Axicabtagene ciloleucel

PLACE OF TECHNOLOGY

If licensed, tafasitamab in combination with lenalidomide will offer an additional treatment option for treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) including DLBCL arising from low-grade lymphoma, and who are not eligible for, or refuse autologous stem cell transplant (ASCT).

CLINICAL TRIAL INFORMATION

Trial	**L-MIND;** NCT02399085; A study to Evaluate the Safety and Efficacy of Lenalidomide With MOR00208 in patients With R-R DLBCL **Phase II - ongoing** **Locations:** 9 EU countries (incl UK) and USA.
Trial design	Open label, single group assignment
Population	N=81; patients with relapsed or refractory DLBCL.
Intervention(s)	Tafasitamab (12mg/kg) and 25mg lenalidomide
Comparator(s)	No comparator
Outcome(s)	Proportion of patients with CR or PR as best response (assessed by independent review committee, IRC) achieved at any time during the study See trial record for full list of other outcomes
Results (efficacy)	IRC assessed complete response and partial response rates were 42.5% and 17.5% respectively, giving an overall response rate of 60%. Investigator assessed median progression free survival and median overall survival were 12.1 months and not reached respectively.[9]
Results (safety)	Tafasitamab + LEN therapy was well tolerated; 77.5% of patients stayed on a LEN dose of ≥20mg/day. Treatment related serious adverse events, mainly infections (10%) or neutropenic fever (5%) occurred in 18.5% of patients.[9]

Trial	NCT016850008; EudraCT 2012-002659-41; Study of Fc-Opimized Anti-CD19 Antibody (MOR208) to Treat Non-Hodgkin's Lymphoma (NHL) **Phase II** **Locations:** 6 EU countries (not incl UK) and USA.
Trial design	Open label, single group assignment
Population	N=92; adults aged over 18 years; histologically confirmed diagnosis of one of the following B-cell lymphomas: follicular lymphoma, mantle cell lymphoma, DLBCL or other indolent NHL.
Intervention(s)	40mg/ml MOR00208 (IV)
Comparator(s)	No comparator
Outcome(s)	Best overall response rate (ORR)

Results (efficacy)	Investigator- assessed ORR in DLBCL, was 26%. Responses lasted lasted ≥12 months in 5/9 responding patients with DLBCL.[40]
Results (safety)	The most common adverse events (any grade) were infusion-related reactions (12%) and neutropenia (12%).[40]

ESTIMATED COST

The estimated cost of tafasitamab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy (GID-TA10580). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Nivolumab for treating relapsed or refractory diffuse large B-cell lymphoma (GID-TA10140). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (GID-TA10463). Expected publication date: April 2020.
- NICE technology appraisal guidance. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (TA567). March 2019.
- NICE technology appraisal guidance. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies. January 2019.
- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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OTHER GUIDANCE

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- European Society for Medical Oncology. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[38]

ADDITIONAL INFORMATION

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