NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Parsaclisib for marginal zone lymphoma – relapsed or refractory

NIHRIO ID	13481	**NICE ID**	10645
Developer/Company	Incyte Corp	**UKPS ID**	N/A

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

SUMMARY

Marginal zone lymphoma (MZL) is a rare group of non-Hodgkin's lymphomas that affect a type of immune cell called B-cells. These MZLs are called low-grade as they are slow-growing and might not always cause symptoms. Some broad symptoms of MZLs are unexplained weight loss, night sweats and fever, however patients are often diagnosed with MZL when they are undergoing tests to investigate something else. Treatment of MZL involves watching and waiting to see how the lymphoma progresses over time with treatment being initiated when the condition worsens (relapses). If the lymphoma persists despite treatment this is known as being refractory. There is currently an unmet need for improved safety of treatment options.

Parsaclisib is an oral selective inhibitor of a protein that can increase B-cell growth and survival, which is a problem in MZL. Parsaclisib is in clinical development for the treatment of patients with relapse or refractory MZL who have never received treatment with a Bruton's tyrosine kinase (BTK) inhibitor or have been previously treated with this.

PROPOSED INDICATION

Treatment of patients with relapsed or refractory marginal zone lymphoma (MZL) who are naive to or were previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.[1]

TECHNOLOGY

DESCRIPTION

Parsaclisib (INCB050465) is a potent and highly selective second-generation inhibitor of phosphatidylinositol 3-kinase δ (PI3Kδ). The PI3Kδ isoform functions as a critical node in signalling networks that regulate B-cell growth and survival, and its aberrant activation is a key event in malignant transformation of B-cells.[2,3]

The constitutive activation of the BCR via the PI3Kδ pathway drives B-cell malignancies. Inhibition of PI3Kδ promotes anti-tumour immunity through regulation of the tumour microenvironment.[2,4-6]

Parsaclisib is in clinical development for relapsed/refractory MZL. In the phase II clinical trial (CITADEL-204; NCT03144674) patients were allocated to receive parsaclisib 20 mg once daily for 8 weeks followed by either 20 mg once weekly (weekly-dosing group) or 2.5 mg (daily-dosing group).[7]

INNOVATION AND/OR ADVANTAGES

Clinical use of first-generation PI3Kδ inhibitors in lymphomas has been limited due to their safety profiles. The structure of parsaclisib differs from first-generation PI3Kδ inhibitors that have entered the clinic. Parsaclisib comprises a monocyclic scaffold with pyrazolopyrimidine substituent compared to a bicyclic scaffold with a purine substituent in first-generation PI3Kδ inhibitors. The safety issues observed with the first-generation inhibitors is believed to be related to these conserved features. As a result, parsaclisib is anticipated to limit off-target toxicity, potentially improving its safety profile.[8,9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Parsaclisib is not currently licenced for any indications in the EU/UK.

Parsaclisib received an orphan drug designation in the EU in July 2019 for the treatment of MZL.[10]

Parsaclisib is in phase 2 clinical development for:[11]

- Autoimmune haemolytic anaemia
- Chronic lymphocytic leukaemia
- Non-Hodgkin's lymphoma

Parsaclisib is in phase 3 clinical development for:[11]

- Myelofibrosis
- Follicular lymphoma/Marginal Zone lymphoma
- Mantle cell lymphoma

PATIENT GROUP

DISEASE BACKGROUND

Lymphoma is the most common type of blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably.[12] These cancerous lymphoma cells can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumour.[13-15] The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B-cells) and T lymphocytes (T-cells).[12]

Marginal zone lymphoma (MZL) is a type of low-grade B-cell NHL that develops from B-cells that are normally found at the edge of areas of lymph node tissue. MZL lymphomas are slow-growing, and many people live with these lymphomas for many years, only needing treatment occasionally, if at all. There are three types of MZL:[12]

- Mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphomas are the most common type of MZL, but are still rare, affecting around 8 in every 100 people diagnosed with NHL. A MALT lymphoma can develop almost anywhere in the body, but it most commonly develops in the stomach (known as gastric MALT lymphoma). There are also non-gastric MALT lymphomas which more commonly affect the salivary glands, skin, gut, and tissue around the eye. MALT lymphomas can occur at any age, but they are most common in people in their mid-60s. MALT lymphoma develops in areas where MALT tissue has formed a response to inflammation caused by a chronic infection, or an autoimmune condition. Gastric MALT lymphoma has been strongly linked to infection by *Helicobacter pylori*. Most people with gastric MALT lymphoma have persistent indigestion, but this is likely to be related to the *H. pylori* infection rather than the lymphoma. Most people with non-gastric MALT lymphoma have no symptoms at all, and the lymphoma is found when they have a test for something else.[13]
- Splenic MZL account for fewer than 2 in 100 cases of NHL. Splenic MZL can affect people of any age but is most common in people in their 60s. In most cases, it is not known what causes splenic MZL. This type of lymphoma is more common in people who have had certain infections, particularly hepatitis C virus. Splenic MZL usually causes enlargement of the spleen, which may cause abdominal pain or discomfort. Unlike most lymphomas splenic MZL does not usually cause swollen lymph nodes. However it can cause unexplained weight loss, night sweats, fever and, in cases where the lymphoma is in the bone marrow, anaemia and thrombocytopenia (blood platelet shortage).[14]
- Nodal MZL account for fewer than 2 in 100 cases of NHL. Nodal MZL can affect people of any age but is most common in people over 50 years, however there is also a rare paediatric variant of nodal MZL. In most cases, it is not known what causes nodal MZL, but it is most common in people who have been infected with hepatitis C virus. Nodal

MZL commonly causes swollen lymph nodes, usually in the neck or groin; the lumps are not usually painful. It can also cause fatigue, unexplained weight loss, night sweats and fever.[15]

Refractory MZL is when the lymphoma does not respond to treatment or when the response to treated is limited, whereas relapsed MZL is when the lymphoma reappears after a period of remission.[16] All MZL types develop slowly and with successful treatment they can be kept under control if there is a relapse, however there is a risk of transformation of the cancer into a faster growing type of lymphoma. This occurs in around 1 in every 10 people with MALT lymphoma, and around 1-2 in every 10 people with nodal MZL or splenic MZL.[13-15]

CLINICAL NEED AND BURDEN OF DISEASE

In the England (2019-20) there were 6,330 finished consultant episodes (FCE) for patients with primary diagnosis of small cell B-cell lymphoma (ICD-10 C83.0, which includes nodal and splenic MZL types[17,18]) resulting in 5,463 day cases and 3,667 FCE bed days.[19]

In England (2019-20) there were 2,388 FCE for patients with a primary diagnosis of MALT lymphoma (ICD-10 C88.4) resulting in 2,032 day cases and 1,370 FCE bed days.[19]

MZL survival statistics (survival for 5 years or more after diagnosis) for patients in one area of England diagnosed between 2004-11 are as follows:[20]

- Stage 1 – 80%
- Stage 2 – 75%
- Stage 3 – more than 50%
- Stage 4 – 65%

MALT lymphomas have a slightly better outcome compared to nodal and splenic MZL with almost 90% of people surviving 5 years or more after diagnosis.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patients with low-grade NHLs are often monitored until treatment is required (known as watch and wait), due to the slower development of the lymphoma.[12-15] Most low-grade NHLs are chronic, meaning they last a long time, with periods of time in spent in remission followed by relapses, during which time the patient will require more treatment.[12]

For recurrent disease, asymptomatic patients may be observed through a "watch-and-wait" strategy. If systemic therapy is required, chemo-immunotherapy can be repeated for patients who showed a durable initial remission of more than 2 years, while autologous transplantation can be considered for fit patients with an aggressive relapse.[21,22]

CURRENT TREATMENT OPTIONS

Whilst no licenced treatments are currently available for relapsed/refractory MZL, a variety of therapies are currently used based on ESMO and NCCN guidelines.

Chemo-immunotherapy options for MZL are the use of rituximab (an antibody therapy) in combination with:[13-15]

- Bendamustine
- Chlorambucil
- Cyclophosphamide, vincristine, and prednisolone (CVP)
- Cyclophosphamide, doxorubicin (or hydroxydaunorubicin), vincristine and prednisolone (CHOP)
- Fludarabine

PLACE OF TECHNOLOGY

If licenced parsaclisib could offer an alternative treatment option for patients with relapsed or refractory MZL who are naive to or were previously treated with a BTK inhibitor.

CLINICAL TRIAL INFORMATION

Trial	**CITADEL-204; NCT03144674;** A Phase 2, Open-Label, 2-Cohort Study of INCB050465, a PI3Kδ Inhibitor, in Subjects With Relapsed or Refractory Marginal Zone Lymphoma With or Without Prior Exposure to a BTK Inhibitor **Phase II –** Active, not recruiting **Location(s):** 6 EU countries, UK, US and other countries **Primary completion date:** January 2022
Trial design	Non-randomised, open-label, sequential assignment.
Population	N=111; aged 18 years and older; histologically confirmed MZL, including extranodal, nodal, and splenic subtypes
Intervention(s)	Patients were allocated to receive parsaclisib 20 mg once daily (QD) for 8 weeks followed by either 20 mg once weekly (weekly-dosing group [WG]) or 2.5 mg QD (daily-dosing group [DG]).[7] Cohort 1: Participants who have received prior ibrutinib. Cohort 2: Participants who have not received a prior BTK inhibitor.
Comparator(s)	No comparator
Outcome(s)	Objective response rate based on Lugano Classification criteria [Time frame: protocol-defined timepoints throughout the study, up to approximately 15 months per participant] Defined as the percentage of participants with a complete response (CR) or partial response (PR) as determined by independent review committee (IRC) assessment.

	See trial record for full list of other outcomes.
Results (efficacy)	From December 2017 to January 17, 2020 (data cut-off), 99 patients (WG, n = 28; DG, n = 71) were treated. Median age was 71 years; 52.5% of the patients were male, 94.9% had an ECOG PS ≤1, and 31.3%, 33.3%, and 35.4% had nodal, extranodal, and splenic MZL, respectively. The median number of prior systemic therapies was 2. At cut-off, 40 (40.4%) patients had discontinued treatment, including 20 (20.2%) for disease progression. The median parsaclisib exposure (range) was 7.5 months (0.4–22.4). At the data cut-off, 94 patients were evaluable for response, including 66 in DG. Median (range) follow-up for the efficacy evaluable population was 11.1 months (1.2–25.0) overall and 9.5 months (1.2–25.0) in DG. The ORR (95% confidence interval [CI]) was 54.3% (43.7–64.6) overall and 57.6% (44.8–69.7) in DG; the ORR (95% CI) was 48.3% (29.4–67.5), 50.0% (31.9–68.1), and 63.6% (45.1–79.6) for patients with nodal, extranodal, and splenic MZL, respectively. The median time to response was 8 weeks. The median DOR (95% CI) was 9.3 months (6.2–not evaluable [NE]) among all responders and 9.4 months (6.0-NE) in DG. The median PFS (95% CI) was 13.8 months (8.8–NE) overall and 11.5 months (8.3-NE) in DG.[7]
Results (safety)	Among the 99 treated patients, the most common treatment-emergent AEs (TEAEs) were diarrhoea (36.4% of patients), cough (18.2%), and rash (14.1%). The most common TEAEs grade ≥3 were neutropenia and diarrhoea (8.1%, each). The most common serious TEAEs were febrile neutropenia and pneumonia (5.1%, each). TEAEs leading to dose interruption or dose reduction occurred in 47.5% and 14.1% of patients, respectively. TEAEs leading to discontinuation occurred in 15.2% of patients; the most common events were diarrhoea (5.1%) and colitis (3.0%). TEAEs leading to death occurred in 4 patients, with 2 events, febrile neutropenia (n = 1) and sepsis (n = 1), deemed treatment related. New or worsening grade ≥3 laboratory test values of clinical interest included increase in alanine/aspartate amino transferase (2.0%/1.0% of patients), and decrease in neutrophil count (13.1%), platelet count (3.0%), and haemoglobin (3.0%).[7]

ESTIMATED COST

The cost of parsaclisib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma (ID1685). Expected date of issue to be confirmed.
- NICE technology appraisal guidance proposed. Mosunetuzumab for treating relapsed or refractory B-cell non-Hodgkin lymphoma (ID3931). Expected date of issue to be confirmed.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- Haematology Expert Advisory Group (EAG) on behalf of NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines (V17). April 2018.

OTHER GUIDANCE

- European Society for Medical Oncology. Marginal Zone Lymphomas: ESMO Clinical Practical Guidelines for diagnosis, treatment and follow-up.[21]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Marginal Zone Lymphomas. March 2015.[22]
- European Society for Medical Oncology. ESMO Consensus Guidelines: Marginal Zone Lymphoma, Mantle Cell Lymphoma, Peripheral T-cell Lymphoma. 2013.[23]

ADDITIONAL INFORMATION

Incyte Corp 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. *A Study of INCB050465 in Subjects With Relapsed or Refractory Marginal Zone Lymphoma (CITADEL-204). Trial ID: NCT03144674*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03144674 [Accessed 17 May 2021].

2 Kang S, Bader AG, Vogt PK. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. *Proc Natl Acad Sci U S A*. 2005 Jan 18;102(3):802-7. Available from: https://doi.org/10.1073/pnas.0408864102.

3 Puri KD, Gold MR. Selective inhibitors of phosphoinositide 3-kinase delta: modulators of B-cell function with potential for treating autoimmune inflammatory diseases and B-cell malignancies. *Front Immunol*. 2012;3:256. Available from: https://doi.org/10.3389/fimmu.2012.00256.

4 Tzenaki N, Papakonstanti EA. p110δ PI3 kinase pathway: emerging roles in cancer. *Front Oncol*. 2013;3:40. Available from: https://doi.org/10.3389/fonc.2013.00040.

5 Gururajan M, Jennings CD, Bondada S. Cutting edge: constitutive B cell receptor signaling is critical for basal growth of B lymphoma. *J Immunol*. 2006 May 15;176(10):5715-9. Available from: https://doi.org/10.4049/jimmunol.176.10.5715.

6 Benschop RJ, Cambier JC. B cell development: signal transduction by antigen receptors and their surrogates. *Curr Opin Immunol*. 1999 Apr;11(2):143-51. Available from: https://doi.org/10.1016/s0952-7915(99)80025-9.

7 Lynch RC, Paneesha S, Avigdor A, McKinney MS, Wahlin BE, Hrom JS, et al. *Phase 2 Study Evaluating the Efficacy and Safety of Parsaclisib in Patients with Relapsed or Refractory Follicular Lymphoma (CITADEL-203).* 2020. Available from: https://ash.confex.com/ash/2020/webprogram/Paper134869.html [Accessed 15 Jun 2021].

8 Forero-Torres A, Ramchandren R, Yacoub A, Wertheim MS, Edenfield WJ, Caimi P, et al. Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies. *Blood*. 2019;133(16):1742-52. Available from: https://doi.org/10.1182/blood-2018-08-867499.

9 Coleman M, Belada D, Casasnovas R-O, Gressin R, Lee H-P, Mehta A, et al. Phase 2 study of parsaclisib (INCB050465), a highly selective, next-generation PI3Kδ inhibitor, in relapsed or refractory diffuse large B-cell lymphoma (CITADEL-202). *Leukemia & Lymphoma*. 2021;62(2):368-76. Available from: https://doi.org/10.1080/10428194.2020.1832660.

10 European Medicines Agency (EMA). *EU/3/19/2185 - Parsaclisib for the treatment of marginal zone lymphoma.* 2019. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3192185 [Accessed 12 May 2021].

11 Clinicaltrials.gov. *Phase II and phase III clinical trials for parsaclisib.* Available from: https://clinicaltrials.gov/ct2/results?term=Parsaclisib&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 03 Jun 2021].

12 Lymphoma Action. *Non-Hodgkin Lymphoma.* 2019. Available from: https://lymphoma-action.org.uk/types-lymphoma/non-hodgkin-lymphoma [Accessed 17 May 2021].

13 Lymphoma Action. *MALT lymphoma (gastric and non-gastric).* 2020. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/malt-lymphoma-gastric-and-non-gastric [Accessed 17 May 2021].

14 Lymphoma Action. *Splenic marginal zone lymphoma.* 2020. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/splenic-marginal-zone-lymphoma [Accessed 17 May 2021].

15 Lymphoma Action. *Nodal marginal zone lymphoma.* 2020. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/nodal-marginal-zone-lymphoma [Accessed 17 May 2021].

16 Lymphoma Research Foundation. *Marginal Zone Lymphoma: Relapsed/Refractory.* 2021. Available from: https://lymphoma.org/aboutlymphoma/nhl/mzl/relapsedmzl/ [Accessed 03 Jun 2021].

17 Orphanet. *Splenic marginal zone lymphoma (ORPHA:86854).* 2007. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=86854 [Accessed 17 May 2021].
18 Orphanet. *Nodal marginal zone B-cell lymphoma (ORPHA:86867).* 2007. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=86867 [Accessed 17 May 2021].
19 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 24 Jun 2021].
20 Cancer Research UK. *Survival - Marginal zone lymphoma.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/survival [Accessed 17 May 2021].
21 Zucca E, Arcaini L, Buske C, Johnson PW, Ponzoni M, Raderer M, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020 Jan;31(1):17-29. Available from: https://doi.org/10.1016/j.annonc.2019.10.010.
22 National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines on Oncology: Non-Hodgkin's Lymphomas: Marginal Zone Lymphomas.* 2015. Available from: https://www2.tri-kobe.org/nccn/guideline/hematologic/nhl/english/mzl.pdf [Accessed 17 May 2021].
23 Dreyling M, Thieblemont C, Gallamini A, Arcaini L, Campo E, Hermine O, et al. ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. *Annals of Oncology*. 2013;24(4):857-77. Available from: https://doi.org/10.1093/annonc/mds643.

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.