

## HEALTH TECHNOLOGY BRIEFING JUNE 2021

### Pirtobrutinib for mantle cell lymphoma

|                   |                       |         |        |
|-------------------|-----------------------|---------|--------|
| NIHRIO ID         | 27486                 | NICE ID | 10525  |
| Developer/Company | Eli Lilly and Company | UKPS ID | 660578 |

|   |   |
|---|---|
| Licensing and market availability plans | Currently in phase III clinical trials. |
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### SUMMARY

Pirtobrutinib is currently in clinical development for mantle cell lymphoma (MCL). MCL is a rare type of non-Hodgkin lymphoma (NHL) that usually behaves like a fast-growing lymphoma. It develops when B-cells, white blood cells, become abnormal. The abnormal B-cells usually build up in lymph nodes, but they can affect other parts of the body. MCL often responds well to frontline chemotherapy but the responses are not durable and often of relatively short duration. Once MCL has entered the relapsed/refractory stage, it becomes more difficult to treat and patients deteriorate at an increasing pace.

Pirtobrutinib is expected to work by reversibly binding to a protein that is critical for the survival and growth of tumour cells; this will inhibit its action, killing tumour cells. Previous inhibitors have been particularly efficacious but due to permanent binding, resistance and intolerance have occurred, so their use must be stopped. In contrast, pirtobrutinib reversibly binds which suggests intolerance and resistance are less likely. If licensed, pirtobrutinib, given orally, will offer an additional second-line or greater treatment for patients with relapsed or refractory MCL who have received prior Bruton's tyrosine kinase (BTK) treatment.

*This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.*

## PROPOSED INDICATION

Treatment of adult patients with previously treated MCL.<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Pirtobrutinib (LOXO-305, LY3527727) is an investigational, highly selective, non-covalent BTK inhibitor that inhibits both wild type (WT) and C481-mutated BTK with equal low nano molar potency. BTK plays a key role in the B-cell antigen receptor signalling pathway, which is required for the development, activation, and survival of normal white blood cells, known as B-cells, and malignant B-cells. BTK is a validated molecular target found across numerous B-cell leukaemia's and lymphomas including chronic lymphocytic leukaemia, Waldenstrom macroglobulinemia, mantle cell lymphoma and marginal zone lymphoma.<sup>2,3</sup>

Pirtobrutinib is currently in clinical development for the treatment of MCL. In clinical trials (NCT04662255, NCT03740529), subjects receive pirtobrutinib administered orally.<sup>1,4</sup>

### INNOVATION AND/OR ADVANTAGES

Currently available BTK inhibitors irreversibly inhibit BTK and the long-term efficacy of these therapies has been limited by acquired resistance, most commonly through BTK C481 mutations, and intolerance, due to off target inhibition of other cellular targets. Pirtobrutinib was designed to reversibly bind BTK, preserve activity in the presence of the C481 acquired resistance mutations, and avoid off-target kinases that have complicated the development of both covalent and investigational non-covalent BTK inhibitors.<sup>2</sup>

A recent phase I/II trial demonstrated favourable efficacy and safety results.<sup>5</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pirtobrutinib does not currently have Marketing Authorisation in the UK/EU.

Pirtobrutinib is currently in phase II/III clinical trials for the treatment of chronic lymphocytic leukaemia, small lymphocytic leukaemia, Waldenström's macroglobulinemia and other B-cell lymphomas.<sup>6</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

MCL is a rare type of NHL that usually behaves like a high-grade lymphoma.<sup>7,8</sup> It develops when B-cells (also called B-lymphocytes) become abnormal. The abnormal B-cells (lymphoma cells) usually build up in lymph nodes, but they can affect other parts of the body. The causes of MCL are mostly unknown.<sup>8</sup>

The most common sign of MCL is painless swelling in neck, armpit or groin caused by lymphoma cells building up in the lymph nodes. Other symptoms include drenching night sweats, high temperatures with no obvious cause, unexplained weight loss. Sometimes other areas of the body may be affected, such as the spleen, bowel, or bone marrow. Depending on

where the lymphoma spreads to, this can cause symptoms such as: loss of appetite, diarrhoea, sickness (nausea), anaemia and bruising or bleeding easily.<sup>8</sup> Rarely, MCL spreads to the brain and spinal cord (the central nervous system or CNS), called secondary CNS lymphoma. This causes symptoms such as headaches, dizziness and confusion.<sup>7</sup>

MCL relapses at some time after treatment in most people. Sometimes, MCL is refractory (does not respond) to the first-line treatment. MCL patients can relapse several times and different treatment may be recommended each time.<sup>7</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

NHL is the 6th most common type of cancer in adults (not counting non melanoma skin cancer) in the UK.<sup>9</sup> There were 12,065 (ICD-10 code C82-85) new cases of NHL in England in 2017.<sup>10</sup>

MCL represents 5%–7% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000 recently.<sup>11</sup> About 500 people are diagnosed with MCL each year in the UK.<sup>7</sup> It mainly occurs in people over the age of 60 and is more common in men than women (3:1 ratio).<sup>8,12</sup>

Regional data from the north east of England collected between 2010 and 2016 indicates that the relative 5-year survival for MCL is 41.9% in the UK.<sup>13</sup>

Hospital admissions data for England in 2019-2020 recorded 8,998 finished consultant episodes (FCE) for MCL (ICD-10 code C83.1), 8,558 hospital admissions and 10,058 FCE bed days.<sup>14</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

A team of specialists, called a multidisciplinary team, will meet to discuss the best possible treatment. The aim of treatment is to get rid of as much of the lymphoma as possible.<sup>8</sup>

Treatment for MCL can be similar to treatment for other types of NHL. Treatment can sometimes get rid of the lymphoma completely. But unfortunately, it can come back fairly soon afterwards. Treatment options include:<sup>15,16</sup>

- Chemotherapy and immunotherapy
- Steroids
- Radiotherapy for people with localised stage I or II mantle cell lymphoma,
- Stem cell transplant
- Less intensive treatment such as bortezomib (a targeted cancer drug), chlorambucil (a chemotherapy drug), ibrutinib.

'Watch and wait' (observation without therapy) may be considered until disease progression for people with clinically non-progressive MCL who are asymptomatic and for whom radiotherapy is not suitable.<sup>16</sup>

### CURRENT TREATMENT OPTIONS

NICE recommends the following treatments for treating relapsed or refractory MCL in people who have received at least one BTK inhibitor therapy:<sup>17,18</sup>

- Autologous anti-CD19-transduced CD3+ cells (for use within the Cancer Drugs Fund)
- Ibrutinib

- Rituximab chemotherapy

## PLACE OF TECHNOLOGY

If licensed, pirtobrutinib will offer an additional second-line or greater treatment for patients with relapsed/refractory MCL.

## CLINICAL TRIAL INFORMATION

|                           |  |
|---------------------------|--|
| <b>Trial</b>              | <b>BRUIN-MCL-321</b> ; <a href="#">NCT04662255</a> ; A Phase 3 Open-Label, Randomized Study of LOXO-305 Versus Investigator Choice of BTK Inhibitor in Patients With Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma<br><b>Phase III</b> – recruiting<br><b>Location(s)</b> : 5 EU countries, UK, US, Canada and other countries<br><b>Primary completion date</b> : August 2024 |
| <b>Trial design</b>       | Randomised, parallel assignment, open label, active-controlled   |
| <b>Population</b>         | N=~500; 18 years and older; Previously treated with at least one prior line of systemic therapy  |
| <b>Intervention(s)</b>    | Pirtobrutinib ; orally   |
| <b>Comparator(s)</b>      | <ul style="list-style-type: none"> <li>• Ibrutinib; orally</li> <li>• Acalabrutinib; orally</li> <li>• Zanabrutinib; orally</li> </ul>   |
| <b>Outcome(s)</b>         | To compare progression-free survival (PFS) of LOXO-305 as monotherapy to investigator choice of covalent BTK inhibitor monotherapy in patients with previously treated MCL [time frame: up to approximately 24 months]. Assessed per Lugano criteria<br><br>See trial record for full list of other outcomes   |
| <b>Results (efficacy)</b> | -  |
| <b>Results (safety)</b>   | -  |

|                     |  |
|---------------------|--|
| <b>Trial</b>        | <b>BRUIN</b> ; <a href="#">NCT03740529</a> ; A Phase 1/2 Study of Oral LOXO-305 in Patients With Previously Treated Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)<br><b>Phase I/II</b> – recruiting<br><b>Location(s)</b> : 3 EU countries, UK, US, Australia and Japan<br><b>Primary completion date</b> : February 2023 |
| <b>Trial design</b> | Non-randomised, parallel assignment, open-label  |
| <b>Population</b>   | N=~860; 18 years and older; Histologically confirmed CLL/SLL, WM, or NHL intolerant to either $\geq 2$ prior standard of care regimens given in combination or sequentially OR have received 1 prior BTK inhibitor-containing regimen when a BTK inhibitor is approved as first line therapy (Phase 1) OR with prior treatment defined by phase 2 cohort                     |

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|---------------------------|---|
| <b>Intervention(s)</b>    | Pirtobrutinib; orally   |
| <b>Comparator(s)</b>      | No comparator   |
| <b>Outcome(s)</b>         | <ul style="list-style-type: none"> <li>• Maximum Tolerated Dose (MTD) [time frame: up to 24 months]</li> <li>• Recommended dose for further study [time frame: up to 24 months]</li> <li>• To assess the preliminary anti-tumour activity of LOXO-305 based on ORR as assessed by an Independent Review Committee (IRC). [time frame: up to 24 months]</li> <li>• To evaluate the safety of LOXO-305 in combination with venetoclax (Arm A) by assessing incidence and severity of treatment-emergent adverse events as determined by CTCAE v5.0 [time frame: up to 24 months]</li> <li>• To evaluate the safety of LOXO-305 in combination with venetoclax and rituximab (Arm B) by assessing incidence and severity of treatment-emergent adverse events as determined by CTCAE v5.0 [time frame: up to 24 months]</li> </ul> <p>See trial record for full list of other outcomes</p> |
| <b>Results (efficacy)</b> | <ul style="list-style-type: none"> <li>• In 121 efficacy evaluable patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) treated with a previous covalent BTK inhibitor (median previous lines of treatment 4), the ORR with pirtobrutinib was 62% (95% CI 53–71). The ORR was similar in CLL patients with previous covalent BTK inhibitor resistance (53 [67%] of 79), covalent BTK inhibitor intolerance (22 [52%] of 42), <i>BTK</i> C481-mutant (17 [71%] of 24) and <i>BTK</i> wild-type (43 [66%] of 65) disease. In 52 efficacy evaluable patients with mantle cell lymphoma (MCL) previously treated with covalent BTK inhibitors, the ORR was 52% (95% CI 38–66). Of 117 patients with CLL, SLL, or MCL who responded, all but eight remain progression-free to date.<sup>5</sup></li> </ul>  |
| <b>Results (safety)</b>   | <ul style="list-style-type: none"> <li>• No dose-limiting toxicities were observed and the maximum tolerated dose was not reached. The recommended phase 2 dose was 200 mg daily.</li> <li>• Adverse events in at least 10% of 323 patients were fatigue (65 [20%]), diarrhoea (55 [17%]), and contusion (42 [13%]). The most common adverse event of grade 3 or higher was neutropenia (32 [10%]). There was no correlation between pirtobrutinib exposure and the frequency of grade 3 treatment-related adverse events. Grade 3 atrial fibrillation or flutter was not observed, and grade 3 haemorrhage was observed in one patient in the setting of mechanical trauma. Five (1%) patients discontinued treatment due to a treatment-related adverse event.<sup>5</sup></li> </ul>   |

## ESTIMATED COST

The cost of pirtobrutinib is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. Venetoclax with ibrutinib for treating relapsed mantle cell lymphoma. (GID-TA10774). Expected publication date TBC.
- NICE technology appraisal. Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma. (TA677). February 2021.
- NICE technology appraisal. Ibrutinib for treating relapsed or refractory mantle cell lymphoma. (TA502). January 2018.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management. (NG52) July 2016.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 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. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

### OTHER GUIDANCE

- NICE pathway. Non-Hodgkin's lymphoma. February 2021.<sup>19</sup>
- British Society for Haematology. Guideline for the management of mantle cell lymphoma. May 2018.<sup>20</sup>
- European Society for Medical Oncology (ESMO). Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. May 2017.<sup>11</sup>

## ADDITIONAL INFORMATION

## REFERENCES

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- Recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT04662255> [Accessed 27 April 2021].
- 2 Eli Lilly and Company. *Loxo Oncology at Lilly Announces Updated Data from the Phase 1/2 BRUIN Clinical Trial for LOXO-305 in Mantle Cell Lymphoma and Non-Hodgkin Lymphomas at the American Society of Hematology (ASH) Annual Meeting*. Available from: <http://lilly.mediaroom.com/2020-12-05-Loxo-Oncology-at-Lilly-Announces-Updated-Data-from-the-Phase-1-2-BRUIN-Clinical-Trial-for-LOXO-305-in-Mantle-Cell-Lymphoma-and-Non-Hodgkin-Lymphomas-at-the-American-Society-of-Hematology-ASH-Annual-Meeting> [Accessed 16 April 2021].
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- 9 Cancer Research UK (CRUK). *What is non-Hodgkin lymphoma?* 2018. Available from: <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/about> [Accessed 16 April 2021].
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**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.**