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# Health Technology Briefing
# July 2024

## Pirtobrutinib for previously treated Bruton tyrosine kinase inhibitor naïve mantle cell lymphoma

| Company/Developer | Eli Lilly and Company Ltd |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 35363 | NICE ID: Not available | UKPS ID: 667745 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Pirtobrutinib is in clinical development for the treatment of previously treated Bruton tyrosine kinase (BTK) inhibitor-naïve mantle cell lymphoma (MCL) in adults. MCL is a rare and aggressive blood cancer that starts in white blood cells (B cells) in the outer edge of the lymph nodes. The abnormal white blood cells start to collect in the lymph nodes or body organs, where they can form painless tumours and begin causing problems within the lymphatic system or the organ where they are growing. MCL is not a curable lymphoma but, in most cases, treatment can put the condition into remission. However, MCL can come back after months or years and, in some cases, treatment might be ineffective. Once MCL has come back, it becomes more difficult to treat and patients deteriorate at an increasing pace. There is a need for novel treatments to improve disease control in patients with MCL.

Pirtobrutinib is a medicine taken orally that is expected to work by blocking BTK, an enzyme that is mostly active in blood cancers and contributes to the growth of the cancer cells. The medicine is expected to slow down or stop the build-up of cancerous B cells in patients with MCL that has come back or not responded to treatment. If licensed, pirtobrutinib will offer an additional treatment option for adults who have been previously treated for MCL but have not received a BTK inhibitor before.

## Proposed Indication

Treatment of adults with relapsed or refractory mantle cell lymphoma (MCL) who have received at least one prior therapy.[a]

## Technology

### Description

Pirtobrutinib (LOXO-305) is an investigational, highly selective, non-covalent BTK inhibitor (BTKi) that inhibits both wild type and C481-mutated BTK with equal low nano molar potency.[1] 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, Waldenström macroglobulinemia, and marginal zone lymphoma.[2]

Pirtobrutinib is currently in clinical development for previously treated BTKi-naïve MCL in adults. In a phase III clinical trial (BRUIN-MCL-321, NCT04662255), 200 mg of pirtobrutinib is administered orally once per day and will be compared against an investigator choice of either ibrutinib, acalabrutinib or zanubrutinib.[3,4]

### Key Innovation

Treatment with covalent BTKis represents an important advance in the management of relapsed or refractory MCL, but these treatments are not curative and many patients ultimately relapse.[4] The long-term efficacy of these therapies can be limited by acquired resistance, most commonly through BTK C481 mutations. In rapidly growing tumours with inherently high rates of BTK turnover, resistance to covalent BTK therapies may be the result of incomplete target inhibition.[2] Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, inhibits both wild type and C481-mutant BTK with equal low nM potency, and has favourable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover.[4]

In a phase I/II trial (NCT03740529) in patients with advanced B-cell malignancies, pirtobrutinib demonstrated promising efficacy in heavily pretreated, poor-prognosis MCL patients following multiple prior lines of therapy, including covalent BTKi.[1] If licensed, pirtobrutinib will offer an additional treatment option for adults with MCL who have been previously treated but are BTKi-naïve.

### Regulatory & Development Status

Pirtobrutinib does not currently have marketing authorisation in the UK for any indication. In the EU, pirtobrutinib has conditional marketing authorisation for MCL.[5]

Pirtobrutinib as a monotherapy is currently in phase II/III clinical development for:[6]

- untreated or previously treated chronic lymphocytic leukemia (CLL);
- untreated or previously treated small lymphocytic lymphoma (SLL);
- previously treated non-Hodgkin lymphoma;

Pirtobrutinib has the following regulatory designations/awards:

- an accelerated approval by the US FDA for relapsed or refractory MCL in January 2023.[7]

[a] Information provided by Eli Lilly and Company Ltd

## Patient Group

### Disease Area and Clinical Need

MCL is a rare type of B cell non-Hodgkin lymphoma (NHL), which is a cancer of the lymphatic system. The lymphatic system has tubes that branch through all parts of the body and carries a colourless liquid called lymph, which contains a high number of white blood cells (lymphocytes) that fight infection. MCL develops when abnormal lymphocytes build up in the lymph nodes or in other body organs, meaning they do not work properly and cannot fight infection like normal white blood cells do. They form tumours and begin causing problems within the lymphatic system or the organ where they are growing.[8] At some point, MCL usually relapses and occasionally does not respond well to first treatment (refractory MCL).[9] The causes of MCL are mostly unknown but it is most common in people over the age of 70, and is more common in men than women.[10] The most common sign of MCL is a painless swelling in the neck, armpit or groin. Other symptoms include: night sweats; fevers; unexplained weight loss; loss of appetite; diarrhoea; sickness; a full feeling in the tummy; and anaemia.[10]

Around 600 people are diagnosed with MCL each year in the UK.[9] Generally for people with MCL, more than 45% survive their cancer for five or more years after diagnosis. For patients younger than 60 years, almost 65% will survive their lymphoma for five years or more after diagnosis. For patients aged 60 to 79 years, almost 55% will survive their lymphoma for five years or more after diagnosis, and for those 80 years or older, around 20% will survive their lymphoma for five years or more after they are diagnosed.[11] In England (2022-23), there were 7,922 finished consultant episodes (FCE) and 7,389 admissions for MCL (ICD-10 code C83.1) resulting in 6,176 day cases and 11,243 FCE bed days.[12]

### Recommended Treatment Options

NICE recommends the following options for treatment of relapsed or refractory MCL:[13]

- ibrutinib, in adults that have had only one previous line of therapy

## Clinical Trial Information

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| Trial | **BRUIN-MCL-321,** NCT04662255, EudraCT 2020-004553-72; 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 (BRUIN MCL-321)<br>**Phase III** –active, not recruiting<br>**Locations:** 14 EU countries, UK, USA, Canada and other countries<br>**Primary completion date:** December 2025 |
| Trial Design | Randomised, parallel assignment, active-controlled, open-label |
| Population | N = 500 (estimated); adults aged 18 years and over with previously treated BTKi-naïve MCL |
| Intervention(s) | 200 mg oral pirtobrutinib once daily.[4] |
| Comparator(s) | Investigator choice of either: 560 mg oral ibrutinib once daily, 100 mg oral acalabrutinib twice daily, or either 160 mg twice daily or 320 mg oral zanubrutinib once daily.[4] |
| Outcome(s) | Primary outcome: to compare progression-free survival (PFS) of pirtobrutinib as monotherapy (arm A) to investigator choice of covalent BTK inhibitor |

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| | monotherapy (arm B) in patients with previously treated MCL [Time frame: up to approximately 24 months]<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of pirtobrutinib is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Pirtobrutinib for treating relapsed or refractory mantle cell lymphoma (GID-TA10858). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Venetoclax with ibrutinib for treating relapsed mantle cell lymphoma (GID-TA10774). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. 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. Clinical Commissioning Policy: Bortezomib for relapsed/refractory mantle cell lymphoma (all ages). 170035P. March 2018.
- NHS England. Clinical Commissioning Policy: Bendamustine with rituximab for relapsed and refractory mantle cell lymphoma (all ages). 170054P. June 2018.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

### Other Guidance

- British Society for Haematology. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. 2023.[14]
- European Society for Medical Oncology. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[15]

## Additional Information

# References


1 Wang M, Shah NN, Alencar AJ, Gerson JN, Patel MR, Fakhri B, et al. LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study. *Blood*. 2020;136(Supplement 1):8-10. Available from: https://doi.org/10.1182/blood-2020-134314.

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*. Press release. Available from: https://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 14 May 2025].

3 ClinicalTrials.gov. *Study of BTK Inhibitor LOXO-305 Versus Approved BTK Inhibitor Drugs in Patients With Mantle Cell Lymphoma (MCL) (BRUIN-MCL-321). Trial ID: NCT04662255*. 2020. Available from: https://clinicaltrials.gov/study/NCT04662255 [Accessed 13 May 2024].

4 Eyre TA, Shah NN, Dreyling M, Jurczak W, Wang Y, Cheah CY, et al. BRUIN MCL-321: phase III study of pirtobrutinib versus investigator choice of BTK inhibitor in BTK inhibitor naive mantle cell lymphoma. *Future Oncology*. 2022;18(36):3961-9. Available from: https://doi.org/10.2217/fon-2022-0976.

5 European Medicines Agency (EMA). *Jaypirca*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/jaypirca.

6 ClinicalTrials.gov. *Search for Pirtobrutinib*. Available from: https://clinicaltrials.gov/search?intr=LOXO-305&spons=Eli%20Lilly%20and%20Company&aggFilters=phase:2%203 [Accessed 14 May 2024].

7 U.S. Food & Drug Administration (FDA). *FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma*. 2023. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma#:~:text=On%20January%2027%2C%202023%2C%20the%20Food%20and%20Drug,lines%20of%20systemic%20therapy%2C%20including%20a%20BTK%20inhibitor. [Accessed 14 May 2024].

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11 Cancer Research UK. *Survival for non-Hodgkin lymphoma*. 2024. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/survival [Accessed 14 May 2024].

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