Health Technology Briefing
December 2023

Pirtobrutinib for untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma

Company/Developer	Eli Lilly and Company Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33803	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pirtobrutinib is currently in clinical development for untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). CLL is a rare type of cancer that affects the blood and bone marrow (the spongy inner part of the bone that produces red and white blood cells). CLL and SLL are the same disease, but whereas in CLL the cancer cells are mostly found in the blood or bone marrow, in SLL they most commonly appear in the lymph nodes. These are small lumps of tissue that contain white blood cells. In both CLL and SLL, too many white blood cells are produced and they develop abnormally. Symptoms include persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising. Typical treatments include chemotherapy and monoclonal antibodies, but since many patients develop resistance to the currently available treatment options, there is a need for novel therapies.

Pirtobrutinib binds to and inhibits an enzyme called Bruton's tyrosine kinase (BTK), which promotes the development and survival of normal and cancerous white blood cells. Pirtobrutinib is highly selective, meaning that it has low effects on other pathways, reducing adverse effects, and overcomes problems with resistance seen in other BTK inhibitors. Pirtobrutinib is taken orally. If licensed, pirtobrutinib would offer a novel treatment option for patients with CLL or SLL who have not previously been treated.

Proposed Indication

Untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL).[1]

Technology

Description

Pirtobrutinib (LOXO-305, LY3527727, Jaypirca)[1,2] is a selective, noncovalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor.[3] BTK inhibitors inactivate BTK by binding to cysteine 481 (C481) in the ATP-binding site of BTK. The expected on-target effect of BTK inhibitors is the inactivation of the BTK enzyme and disruption of B-cell receptor (BCR) signalling. Because BCR signalling is activated in CLL/SLL, its disruption has the potential to halt the progression of the disease. It is also hypothesised that there is an indirect effect of BCR signalling blockade on the tumour microenvironment, resulting in a pro-apoptotic environment less favourable for tumour growth.[4]

Pirtobrutinib is currently in clinical development for untreated CLL or SLL. In the phase III clinical trial (NCT05023980), pirtobrutinib is administered orally.

Key Innovation

There is growing concern for the development of resistance to covalent BTK inhibitors, leading to treatment discontinuation in a large majority of patients.[5] This resistance is due to BTK mutations in the C481 position, which prevent irreversible (covalent) drug binding.[6] Pirtobrutinib was therefore developed to noncovalently (reversibly) bind BTK, to preserve activity in the presence of acquired C481 resistance mutations.[7] Pirtobrutinib is the first noncovalent BTK inhibitor that has shown a potential benefit for patients who have been previously exposed and treated with covalent BTK inhibitors,[5,8] and researchers are recognising pirtobrutinib for its ability to treat recurrent or relapsing CLL.[5] In addition, pirtobrutinib has been found to be 300 times more selective in BTK inhibition versus 98% of other kinases tested in preclinical studies,[9] reducing off-target adverse effects[6]

If licensed, pirtobrutinib will offer a novel treatment option for patients with CLL or SLL who have not previously been treated.

Regulatory & Development Status

Pirtobrutinib currently has Marketing Authorisation in the EU for relapsed or refractory mantle cell lymphoma.[10]

Pirtobrutinib is also in phase II/III clinical development for several indications, some of which are:[11]

- B-cell leukaemia
- Waldenström macroglobulinemia
- Lymphoid leukaemia
- Non-Hodgkin leukaemia

Patient Group

Disease Area and Clinical Need

CLL is a rare type of cancer that affects the blood and bone marrow, and it usually progresses slowly. Although it cannot usually be cured, it can be managed with treatment. The risk increases with age and it

is very rare in people under 40. Although the cause is unclear, the risk increases with a family history of CLL.[12] In CLL, the bone marrow produces too many lymphocytes that are not fully developed and do not work properly. Over time this can cause a range of problems, such as an increased risk of picking up infections, persistent tiredness, swollen glands in the neck, armpits or groin, and unusual bleeding or bruising.[13] CLL and SLL are the same disease, but whereas in CLL the cancer cells are mostly found in the blood or bone marrow, in SLL they most commonly appear in the lymph nodes.[14]

Around 3,800 people are diagnosed with CLL in the UK each year.[15] There are around 980 CLL deaths in the UK every year (2017-2019). Mortality rates for CLL in the UK are highest in people aged 90+ (2017-2019). Since the early 1990s, CLL incidence rates have increased by a sixth (17%) in the UK. The age standardised incidence rate of lymphoid leukaemia in England is 10.7 and 5.6 per 100,000 amongst males and females respectively.[16] For lymphoid leukaemia, in England (2022-23) there were 60,888 finished consultant episodes (FCEs) and 58,592 admissions (ICD-10 code C91), which resulted in 50,127 day cases and 68,261 FCE bed days. In England (2017), there were 4,226 patients diagnosed with lymphoid leukaemia and 1,085 deaths registered where lymphoid leukaemia was the underlying cause.[16]

Recommended Treatment Options

NICE currently recommends the following for untreated CLL:[17-20]

- Ibrutinib with venetoclax
- Venetoclax with obinutuzumab
- Obinutuzumab with chlorambucil
- Bendamustine

Clinical Trial Information

Trial	**BRUIN CLL-313;** NCT05023980, EudraCT 2021-001234-20; A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab in Untreated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma **Phase III:** recruiting **Locations:** Eleven EU countries, US, UK and eight other countries **Primary completion date:** November 2024
Trial Design	Randomised, parallel assignment, open label
Population	N = 250 (estimated); all sexes; adults aged over 18 years; confirmed diagnosis of CLL/SLL.
Intervention(s)	Pirtobrutinib administered orally
Comparator(s)	• Bendamustine administered intravenously • Rituximab administered intravenously
Outcome(s)	Primary outcome measure: • To evaluate progression-free survival (PFS) of pirtobrutinib (Arm A) compared to bendamustine and rituximab (Arm B) [time frame: up to approximately 5 years] See trial record for full list of outcomes.
Results (efficacy)	-

Results (safety)	-

Estimated Cost

The cost of pirtobrutinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Zanubrutinib for untreated chronic lymphocytic leukaemia (GID-TA10966). Expected date of issue to be confirmed.
- NICE technology appraisal. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia (TA891). May 2023.
- NICE technology appraisal. Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (TA663). December 2020.
- NICE technology appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343). June 2015.
- NICE technology appraisal. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia. (TA216). February 2011.
- NICE technology appraisal. Rituximab for the first-line treatment of chronic lymphocytic leukaemia (TA174). July 2009.

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.

Other Guidance

- Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H et al. Guideline for the treatment of chronic lymphocytic leukaemia. 2022.[21]
- Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G et al. NCCN Guidelines Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022. 2022.[22]
- Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[23]
- Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner et al. H. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. 2018.[24]

Additional Information

Eli Lilly and Company Ltd 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 Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab (BR) in Untreated Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (BRUIN CLL-313)*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05023980 [Accessed 30 October 2023].

2 Eli Lilly and Company Ltd. *U.S. FDA Approves Jaypirca™ (pirtobrutinib), the First and Only Non-Covalent (Reversible) BTK Inhibitor, for Adult Patients with Relapsed or Refractory Mantle Cell Lymphoma After at Least Two Lines of Systemic Therapy, Including a BTK Inhibitor*. 2023. Available from: https://investor.lilly.com/news-releases/news-release-details/us-fda-approves-jaypircatm-pirtobrutinib-first-and-only-non [Accessed 20 November 2023].

3 Mato AR, Woyach JA, Brown JR, Ghia P, Patel K, Eyre TA, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. *New England Journal of Medicine*. 2023;389(1):33-44. Available from: https://doi.org/10.1056/NEJMoa2300696.

4 St-Pierre F, Ma S. Use of BTK Inhibitors in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): A Practical Guidance. *Blood and Lymphatic Cancer*. 2022;12:81-98. Available from: https://doi.org/10.2147/blctt.S326627.

5 Pharmacy Times. *Oncology Overview: Pirtobrutinib—A New BTK Inhibitor*. 2022. Available from: https://www.pharmacytimes.com/view/oncology-overview-pirtobrutinib-a-new-btk-inhibitor [Accessed 7 November 2023].

6 Wang ML, Jurczak W, Zinzani PL, Eyre TA, Cheah CY, Ujjani CS, et al. Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma. *Journal of Clinical Oncology*. 2023;41(24):3988-97. Available from: https://doi.org/10.1200/jco.23.00562.

7 Eli Lilly and Company Ltd. *Loxo@Lilly Presents Updated Pirtobrutinib Data from the Phase 1/2 BRUIN Clinical Trial at the 2022 American Society of Hematology Annual Meeting*. 2022. Available from: https://investor.lilly.com/news-releases/news-release-details/loxolilly-presents-updated-pirtobrutinib-data-phase-12-bruin [Accessed 7 November 2023].

8 OncLive. *Pirtobrutinib, Liso-Cel Could Expand Treatment Arsenal for Relapsed/Refractory CLL*. 2023. Available from: https://www.onclive.com/view/pirtobrutinib-liso-cel-could-expand-treatment-arsenal-for-relapsed-refractory-cll [Accessed 20 November 2023].

9 Jensen JL, Mato AR, Pena C, Roeker LE, Coombs CC. The potential of pirtobrutinib in multiple B-cell malignancies. *Ther Adv Hematol*. 2022;13:20406207221101697. Available from: https://doi.org/10.1177/20406207221101697.

10 European Medicines Agency. *Jaypirca*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/jaypirca [Accessed 1 November 2023].

11 Clinicaltrials.gov. *Pirtobrutinib | Recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Phase 2, 3 | Industry*. 2023. Available from: https://classic.clinicaltrials.gov/ct2/results?term=pirtobrutinib&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=Intr&rslt=&phase=1&phase=2&fund=2&Search=Apply [Accessed 1 November 2023].

12 National Health Service (NHS). *What is chronic lymphocytic leukaemia?* 2023. Available from: https://www.nhs.uk/conditions/chronic-lymphocytic-leukaemia/ [Accessed 2 November 2023].

13 NHS Inform. *Chronic lymphocytic leukaemia*. 2023. Available from: https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-adults/chronic-lymphocytic-leukaemia [Accessed 2 November 2023].

14 Heathline. *Chronic Lymphocytic Leukemia (CLL) vs. Small Lymphocytic Lymphoma (SLL)*. 2022. Available from: https://www.healthline.com/health/leukemia/cll-vs-sll [Accessed 2 November 2023].
15 Cancer Research UK. *What is chronic lymphocytic leukaemia (CLL)?* 2021. Available from: https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/about [Accessed 2 November 2023].
16 Office for National Statistics (ONS). *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 2 November 2023].
17 National Institute for Health and Care Excellence (NICE). *Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia*. 2023. Available from: https://www.nice.org.uk/guidance/ta891/chapter/1-Recommendations [Accessed 2 November 2023].
18 National Institute for Health and Care Excellence (NICE). *Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia*. 2020. Available from: https://www.nice.org.uk/guidance/ta663 [Accessed 20 November 2023].
19 National Institute for Health and Care Excellence (NICE). *Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia*. 2015. Available from: https://www.nice.org.uk/guidance/ta343 [Accessed 20 November 2023].
20 National Institute for Health and Care Excellence (NICE). *Bendamustine for the first-line treatment of chronic lymphocytic leukaemia*. 2011. Available from: https://www.nice.org.uk/guidance/ta216 [Accessed 20 November 2023].
21 Walewska R, Parry-Jones N, Eyre TA, Follows G, Martinez-Calle N, McCarthy H, et al. Guideline for the treatment of chronic lymphocytic leukaemia. *British Journal of Haematology*. 2022;197(5):544-57. Available from: https://doi.org/10.1111/bjh.18075.
22 Wierda WG, Brown J, Abramson JS, Awan F, Bilgrami SF, Bociek G, et al. NCCN Guidelines® Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022: Featured Updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network*. 2022;20(6):622-34. Available from: https://doi.org/10.6004/jnccn.2022.0031.
23 Eichhorst B, Robak T, Montserrat E, Ghia P, Niemann CU, Kater AP, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2021;32(1):23-33. Available from: https://doi.org/10.1016/j.annonc.2020.09.019.
24 Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-60. Available from: https://doi.org/10.1182/blood-2017-09-806398.

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