NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# July 2023

## Tazemetostat for treating relapsed or refractory follicular lymphoma after two therapies

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

| NIHRIO ID: 11339 | NICE TSID: Not applicable | UKPS ID: 670690 |
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## Licensing and Market Availability Plans

Tazemetostat is currently in phase I/II clinical trials.

## Summary

Tazemetostat is in clinical development for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least two prior treatments. Follicular lymphoma is a cancer of a type of white blood cell called B lymphocytes, or B cells. In follicular lymphoma, B cells multiply quickly and live for too long, so there are too many of them in the lymph nodes. The first sign of the disease is usually a lump in the neck, under the arm or in the groin area, caused by an enlarged lymph node. Patients may also have fever, weight loss, tiredness, and night sweats. If a person has successful treatment but the follicular lymphoma returns after more than six months, this is known as relapsed lymphoma, while if it returns within six months, it is known as refractory lymphoma. Most patients will experience relapse and subsequent treatments are not as efficient nor well tolerated as the first ones, hence the need for more effective treatment options for the relapsed or refractory disease.

Tazemetostat is an oral medication designed to block a protein called EZH2. EZH2 has an essential role in follicular lymphoma and is also altered in some patients with the condition, encouraging abnormal growth and development of B cells. By blocking the altered EZH2 protein, tazemetostat is expected to lead to the death of lymphoma cells and thus stop the spread of the lymphoma. If licensed, tazemetostat would provide a novel treatment option for relapsed or refractory follicular lymphoma.

## Proposed Indication

Treatment of relapsed or refractory follicular lymphoma in adult patients who have had at least two prior systemic therapies.[1,2]

## Technology

### Description

Tazemetostat (Tazverik; EPZ-6438; E7438) is an orally-available EZH2 (enhancer of zeste homolog 2) inhibitor.[3] EZH2 is a histone methyltransferase that when hyperactivated, enhances the proliferation of B cells, preventing them for exiting the germinal centre and, thus, promoting lymphomagenesis.[3] Follicular lymphoma develops when the body produces abnormal B lymphocytes, a type of white blood cell that usually aids in fighting infection.[4] Tazemetostat works by inhibiting both mutant and wild-type forms of EZH2 to induce cell cycle arrest and apoptosis of lymphoma cells.[3]

Tazemetostat is in clinical development for the treatment of adult patients with relapsed/refractory follicular lymphoma, who have had at least two prior systemic therapies. In the phase I/II clinical trial (NCT01897571), patients were administered 800mg of tazemetostat orally twice daily in continuous 28-day cycles.[1,5]

### Key Innovation

For most patients with follicular lymphoma who experience relapse, subsequent treatments are not as efficient or well-tolerated as first-line treatments. An important driver of follicular lymphoma is a gene called EZH2 that makes B cells proliferate, either because of mutations that increase its activity or because of a net increase in its concentration in lymphoma cells. Tazemetostat was designed to inhibit EZH2 protein and thus stop lymphoma cell growth in patients who have experienced relapse after previous treatments regardless of EZH2 mutation status, or for patients with follicular lymphoma who have no other therapeutic options.[3] If licensed, tazemetostat will offer a novel treatment option for patients with relapsed or refractory follicular lymphoma who have had at least two lines of prior treatment.

### Regulatory & Development Status

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

Tazemetostat has the following regulatory designations/awards:[6,7]

- an orphan drug in the EU in 2018 for the treatment of follicular lymphoma
- accelerated approval by the US FDA in June 2020 for adult patients with relapsed or refractory follicular lymphoma whose tumours are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

Tazemetostat monotherapy is currently in phase II/III clinical trials for:[8]

- solid tumours harbouring an ARID1A mutation
- malignant peripheral nerve sheath tumours
- soft tissue sarcoma

## Patient Group

## Disease Area and Clinical Need

Follicular lymphoma is the most common type of non-Hodgkin lymphoma.[9] It develops when the body makes abnormal B lymphocytes, a type of white blood cell that fights infection.[4] Follicular lymphoma is slow growing, meaning that symptoms develop gradually over time. Some people have a few symptoms but others have none.[10] The most common symptom of follicular lymphoma is one or more painless swellings in the neck, armpit or groin. Other, more general symptoms include heavy sweating at night, high temperatures that come or go without any obvious cause, unexplained weight loss, frequent infections or difficulty getting over infections, and fatigue.[4,10] Most people live with follicular lymphoma for many years, with periods where treatment is not required and other times when symptoms get worse and more treatment is needed.[10] If a lymphoma returns more than six months after previous successful treatment, this is known as relapsed lymphoma, whereas lymphoma that returns within six months of treatment is termed refractory.[11] In most cases, there is no known cause for follicular lymphoma but some genetic changes are common. It can develop at any age, but it is more common in people over 60 years.[10]

Of all people with non-Hodgkin lymphoma in the UK, around 19% have follicular lymphoma.[4] It has been estimated that around 2,600 people are diagnosed with follicular lymphoma every year in the UK.[4] In England in 2021-22, there were 21,163 finished consultant episodes (FCE) and 20,446 admissions for follicular lymphoma (ICD10 code C82), which resulted in 11,593 FCE bed days and 18,999 day cases.[12]

## Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options for relapsed or refractory follicular lymphoma:[13]

- Rituximab in combination with chemotherapy for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma.
- Rituximab monotherapy for maintenance therapy in people with stage III or IV follicular lymphoma in remission.
- Rituximab monotherapy for treatment in people with stage III or IV follicular lymphoma who have exhausted all other treatment options.
- Autologous stem cell transplantation for consolidation in people who have follicular lymphoma in second or subsequent remission who have not previously had a transplant but are considered fit enough for transplantation.

## Clinical Trial Information

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| Trial | NCT01897571; An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumours or With B-cell Lymphomas and Tazemetostat in Combination With Prednisolone in Subjects With Diffuse Large B Cell Lymphoma<br>**Phase I/II** - Completed<br>**Location(s)** – Six EU countries, UK, USA, Canada, Australia and Taiwan<br>**Study completion date:** November 2021 |
| Trial Design | Single group assignment, non-randomised, open-label |
| Population | N = 420 (estimated), aged 16 years and older; all sexes; subjects with histologically-confirmed relapsed or refractory diffuse large B-cell lymphoma following at least two lines of prior therapy |
| Intervention(s) | Tazemetostat (oral) 800 mg twice per day in continuous 28-day cycles.[5] |

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| Comparator(s) | No comparator |
| Outcome(s) | Primary outcome measures:<br>• Maximum tolerated dose (MTD) (Phase 1 only) [Time frame: 28 day cycle of therapy]<br>• Objective response rate (ORR; complete response + partial response [CR + PR]) (Phase 2) [Time frame: Every 8 weeks or sooner, if clinically indicated, until documentation of disease]<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | Between July 9, 2015, and May 24, 2019, 99 patients were enrolled in the study. At data cut-off for the analysis (Aug 9, 2019), the objective response rate was 69% (95% confidence interval 53-81; 31 of 45 patients) in the EZH2 mutant cohort and 35% (95% confidence interval 23-49; 19 of 54 patients) in the EZH2 wild-type cohort. Median duration of response was 10·9 months (95% CI 7·2–not estimable [NE]) in the EZH2mutant cohort and 13·0 months (5·6–NE) in the EZH2 wild-type cohort; median progression-free survival was 13·8 months (10·7–22·0) and 11·1 months (3·7–14·6).[5] |
| Results (safety) | Among all 99 patients, treatment-related grade 3 or worse adverse events included thrombocytopenia (three [3%]), neutropenia (three [3%]), and anaemia (two [2%]). Serious treatment-related adverse events were reported in four (4%) of 99 patients. There were no treatment-related deaths.[5] |

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| Trial | **TRuST,** NCT02875548; Tazemetostat Rollover Study (TRuST): An Open-Label, Rollover Study<br>**Phase I/II** – active, not recruiting<br>**Location(s)** – Five EU countries, UK, USA and Australia<br>**Primary completion date:** December 2024 |
| Trial Design | Single group assignment, open-label |
| Population | N = 100 (estimated); aged 18 years or older; all sexes; subjects currently receiving tazemetostat either as monotherapy or in combination with other approved drug(s) or investigational agent(s) in an antecedent study; and has a life expectancy of three months or more |
| Intervention(s) | Tazemetostat at the same dose and schedule as specified in their antecedent tazemetostat protocol. |
| Comparator(s) | No comparator |
| Outcome(s) | Primary outcome measures:<br><br>• Percentage of participants with adverse events and treatment-emergent adverse events [Time frame: until end of study, an average of seven years]<br>• Duration of study drug exposure [Time frame: until end of study, an average of seven years] |

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| | See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of tazemetostat is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Ibrutinib for treating relapsed or refractory follicular lymphoma (GID-TA10223). Expected date of issue to be confirmed.
- NICE technology appraisal. Axicatagene ciloleucel for treating relapsed or refractory follicular lymphoma (TA894). June 2023.
- NICE technology appraisal. Mosunetuzumab for treating relapsed or refractory follicular lymphoma (GID-TA10816). May 2023.
- NICE technology appraisal. Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab (TA629). May 2020.
- NICE technology appraisal. Lenalidomide with rituximab for previously treated follicular lymphoma (TA627). April 2020.
- NICE technology appraisal. Idelalisib for treating refractory follicular lymphoma (TA604). October 2019.
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE clinical guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NJS Standard Contact for Cancer: Chemotherapy (Adult). B15/S/a.

### Other Guidance

- Dreyling M, Ghielmini M, Rule S, Salles G, Ladetto M, Tonino SH, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2021.[14]
- McNamara C, Montono S, Eyre TA, Ardeshna K, Burton C, Illidge T, et al. The investigation and management of follicular lymphoma. 2020.[15]
- Bron D, Maerevoet M, Van den Neste E, Delrieu V, Offner F, Schroyens W, et al. BHS guidelines for the treatment of marginal zone lymphomas: 2018 update. 2019.[16]
- University College London Hospitals NHS Foundation Trust. Pan-London Haemato-Oncology Clinical Guidelines. Lymphoid Malignancies Part 3: Follicular Lymphoma. 2018.[17]

## Additional Information

## References


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5 Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *The Lancet Oncology*. 2020;21(11):1433-42. Available from: https://doi.org/10.1016/S1470-2045(20)30441-1.

6 European Medicines Agency. *EU/3/18/2005: Orphan designation for the treatment of follicular lymphoma*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-18-2005 [Accessed 4 May 2023].

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8 ClinicalTrials.gov. *Search for: Tazemetostat | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. 2023. Available from: https://clinicaltrials.gov/ct2/results?term=Tazemetostat&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 12 June 2023].

9 Cancer Research UK. *Low grade NHL*. 2020. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/low-grade [Accessed 24 May 2023].

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