27 February 2025
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report on variation of extension of indication

Invented name: Jaypirca

International non-proprietary name: Pirtobrutinib

Procedure No. EMEA/H/C/005863/II/0002

Marketing authorisation holder (MAH) Eli Lilly Nederland B.V.

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

**1. Background information on the procedure ..... 8**
1.1. Type II variation ..... 8
1.2. Steps taken for the assessment of the product ..... 9

**2. Scientific discussion ..... 10**
2.1. Introduction ..... 10
2.1.1. Problem statement ..... 10
2.1.2. About the product ..... 13
2.1.3. General comments on compliance with GCP ..... 13
2.2. Non-clinical aspects ..... 13
2.2.1. Ecotoxicity/environmental risk assessment ..... 13
2.2.2. Discussion on non-clinical aspects ..... 15
2.2.3. Conclusion on the non-clinical aspects ..... 15
2.3. Clinical aspects ..... 15
2.3.1. Introduction ..... 15
2.3.2. Pharmacokinetics ..... 17
2.3.3. Pharmacodynamics ..... 20
2.3.4. Discussion on clinical pharmacology ..... 25
2.3.5. Conclusions on clinical pharmacology ..... 25
2.4. Clinical efficacy ..... 25
2.4.1. Dose response study ..... 25
2.4.2. Main study ..... 26
2.4.3. Discussion on clinical efficacy ..... 65
2.4.4. Conclusions on the clinical efficacy ..... 70
2.5. Clinical safety ..... 70
2.5.1. Discussion on clinical safety ..... 84
2.5.2. Conclusions on clinical safety ..... 88
2.5.3. PSUR cycle ..... 88
2.6. Risk management plan ..... 88
2.7. Update of the Product information ..... 91
2.7.1. User consultation ..... 91

**3. Benefit-Risk Balance ..... 91**
3.1. Therapeutic Context ..... 91
3.1.1. Disease or condition ..... 91
3.1.2. Available therapies and unmet medical need ..... 91
3.1.3. Main clinical studies ..... 92
3.2. Favourable effects ..... 92
3.3. Uncertainties and limitations about favourable effects ..... 92
3.4. Unfavourable effects ..... 93
3.5. Uncertainties and limitations about unfavourable effects ..... 93
3.6. Effects Table ..... 93
3.7. Benefit-risk assessment and discussion ..... 94
3.7.1. Importance of favourable and unfavourable effects ..... 94
3.7.2. Balance of benefits and risks ..... 95

3.8. Conclusions ..... 95

**4. Recommendations ..... 95**

# List of abbreviations

| | |
|---|---|
| AE | adverse event |
| AIHA | autoimmune hemolytic anemia |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ASCO | American Society Committee Organization |
| AST | aspartate aminotransferase |
| AUC | area under the concentration versus time curve |
| BBB | bundle branch block |
| BCR | B cell receptor |
| Bcl2 | B cell lymphoma 2 |
| BID | twice a day |
| BOR | best overall response |
| BendaR | bendamustine with rituximab |
| BSA | body surface area |
| BTK | Bruton's tyrosine kinase |
| CXDX | Cycle X Day X |
| C481 | cysteine residue at position 481 |
| CAR-T | chimeric antigen receptor-modified T cells |
| cfDNA | cell free DNA |
| CI | confidence interval |
| CLL/SLL | chronic lymphocytic leukemia/small lymphocytic lymphoma |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| COPD | chronic obstructive pulmonary disease |
| CHMP | Committee for Medicinal Products for Human Use |
| CR | complete remission |
| CRi | complete remission with incomplete marrow recovery |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria in Adverse Events |
| CTFG | Clinical Trial Facilitation Group |
| CYP | cytochrome P450 |
| CYP3A4 | cytochrome P450 3A4 |

| | |
|---|---|
| DCO | data cut-off |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| EC | European Commission |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EFS | event free survival |
| EORTC | European Organisation for Research and Treatment of Cancer Quality of Life questionnaire |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 |
| EOT | End of Treatment |
| ePRO | electronic patient reported outcome |
| EQ-5D-5L | 5-level-Euro quality of life questionnaire |
| GCP | Good Clinical Practice |
| GnRH | gonadotropin-releasing hormone |
| HBc | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| IB | Investigator’s Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IdelaR | idelalisib with rituximab |
| IGHV | immunoglobulin heavy chain variable region gene |
| IgM | immunoglobulin M |
| IRC | Independent Review Committee |

| | |
|---|---|
| ITP | idiopathic thrombocytopenic purpura |
| ITT | intention to treat |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous(ly) |
| IVIG | intravenous immoglobulin |
| iwCLL | International Workshop on Chronic Lymphocytic Leukemia |
| IXRS | interactive voice/web response system |
| LHRH | luteinizing hormone-releasing hormone |
| LTFU | Long-Term Follow-up |
| LVEF | left ventricular ejection fraction |
| MCL | mantle cell lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | minimal residual disease |
| MRI | magnetic resonance imaging |
| MTD | maximal tolerated dose |
| MZL | marginal zone lymphoma |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NHL | non-Hodgkin lymphoma |
| nPR | nodular partial remission |
| ORR | overall response rate |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PD | progressive disease; disease progression |
| PFS | progression-free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| PI | product information |
| PLCg2 | phospholipase C gamma 2 |
| PO | per os, oral |
| PR | partial remission |
| PR-L | PR with lymphocytosis |

| | |
|---|---|
| PRO | patient reported outcomes |
| Q2W | every 2 weeks |
| Q4W | every 4 weeks |
| Q12W | every 12 weeks |
| Q24W | every 24 weeks |
| QD | once daily |
| QoL | quality of life |
| QTc | corrected QT interval |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RBC | red blood cell |
| RMP | Risk Management Plan |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| RSI | Request for Supplementary Information |
| r/r | relapsed/refractory |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCT | stem cell transplantation |
| SERD | selective estrogen receptor degrader |
| SERM | selective estrogen receptor modulator |
| SFU | Safety Follow-up |
| SmPC | Summary of Product Characteristics |
| SoA | Schedule of Assessments |
| SPM | second primary malignancy |
| SRC | Safety Review Committee |
| TEAE | Treatment-emergent adverse event |
| TEC | intracellular non-receptor tyrosine kinases |
| TTNT | time to next treatment |
| TTW | time to worsening |
| US | United States |
| ULN | upper limit of normal |
| WM | Waldenström's macroglobulinemia |
| WOCBP | woman of childbearing potential |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 11 March 2024 an application for a variation.

The following variation was requested:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with chronic lymphocytic leukemia (CLL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor for JAYPIRCA, based on interim results from study LOXO-BTK-20020 (BRUIN CLL-321); this is a phase 3 open-label, randomized study of LOXO-305 versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated CLL/small lymphocytic lymphoma (SLL).
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0197/2021 on the granting of a (product-specific) waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

## *MAH request for additional data exclusivity*

The MAH requested consideration of its application in accordance with Article 10(5) of Directive 2001/83/EC - one year of data exclusivity for a new indication.

During the evaluation of the procedure, the MAH withdrew this request.

## *Scientific advice*

The MAH received Scientific Advice from the CHMP on 17 September 2020

(EMEA/H/SA/4588/1/2020/II.) The Scientific Advice pertained to clinical aspects of the dossier.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Edward Laane

| Timetable | Actual dates |
|---|---|
| Submission date | 11 March 2024 |
| Start of procedure: | 30 March 2024 |
| CHMP Rapporteur Assessment Report | 31 May 2024 |
| PRAC Rapporteur Assessment Report | 3 June 2024 |
| CHMP Co-Rapporteur Assessment | 10 June 2024 |
| Updated PRAC Rapporteur Assessment Report | 11 June 2024 |
| PRAC Outcome | 13 June 2024 |
| CHMP members comments | 17 June 2024 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 20 June 2024 |
| Request for supplementary information (RSI) | 27 June 2024 |
| CHMP Rapporteur Assessment Report | 2 January 2025 |
| PRAC Rapporteur Assessment Report | 6 January 2025 |
| PRAC members comments | 8 January 2025 |
| Updated PRAC Rapporteur Assessment Report | 9 January 2025 |
| PRAC Outcome | 16 January 2025 |
| CHMP members comments | 20 January 2025 |
| Updated CHMP Rapporteur Assessment Report | 23 January 2025 |
| Request for supplementary information (RSI) | 30 January 2025 |
| CHMP Rapporteur Assessment Report | 12 February 2025 |
| CHMP members comments | 17 February 2025 |
| Updated CHMP Rapporteur Assessment Report | 20 February 2025 |
| Opinion | 27 February 2025 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

Jaypirca as monotherapy is currently conditionally approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.

The MAH is seeking an extension of the marketing authorization (MA) for the following indication:

"*Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.*"

### *Disease or condition*

CLL and SLL are incurable B-cell malignancies considered distinct clinical manifestations of the same biologic disease by the World Health Organization (WHO) classification and are managed similarly and are collectively referred to as CLL (NCCN 2023; Eichhorst et al. 2015; Zelenetz et al. 2015;).

In this report, the terms CLL/SLL and CLL are used interchangeably.

### *Epidemiology*

With an estimated incidence of 4.7 new cases per 100,000 individuals, CLL is the most common form of chronic leukaemia in the US and Europe (Bosch and Dalla-Favera 2019). According to data from the cancer registries across Europe, the crude rate (per 100,000) of CLL from the years 2000 to 2002 was 4.92 (male: 5.87; female 4.01) (Sant et al. 2010). Using data from the Global Cancer Incidence and Mortality (GLOBOCAN)/European Cancer Information System (ECIS) and the Nordic database (NORDCAN), the overall complete prevalence of CLL/SLL in the EU was estimated to be approximately 5 per 10,000 (Danckert et al. 2019; Ferlay et al. 2020).

CLL incidence increases steadily with age without plateauing and is rare in people below 50 years of age. The median age of CLL diagnosis is 70 years, with an expected variation among countries reflecting differences in age distribution (Yang et al. 2015).

More common in men compared to women with a ratio of approximately 2:1 regardless of ethnicity (Montserrat et al. 2002; Yang et al. 2015), CLL also presents a geographic variation in its incidence, with the highest incidence rates among the White populations of North America, Europe, and Israel versus the lowest rates among Asian countries, particularly Japan and China (Ruchlemer and Polliack 2013). A similar racial/ethnic pattern has been observed within a country. CLL in Asian populations appears to have different features from CLL in persons of predominately European descent. Individuals of Asian descent diagnosed with CLL are typically of a younger age, have atypical morphologic and immunologic features, an increased proportion of IGHV mutations and re-arrangements and briefer freedom-from-progression compared to individuals predominately of European descent with CLL (Yang et al. 2015).

CLL has the highest incidence of familial association among leukaemias, with first-degree relatives having more than 8-fold higher likelihood of developing the disease (Chiorazzi et al. 2021).

Additionally, exposure to certain pesticides, specifically Agent Orange used during the Vietnam War, and radon has been associated with the development of CLL (Chiorazzi et al. 2021).

## *Clinical presentation and prognosis*

CLL is characterised by the clonal proliferation and accumulation of mature, typically CD5-positive B cells within the blood, bone marrow, lymph nodes, and spleen (Hallek et al. 2019). The presentation and clinical course are highly variable, ranging from asymptomatic, indolent disease that may never require therapy (in approximately 30% of patients) to active disease in patients who have inflammatory or B-cell symptoms (that is, weight loss, night sweats, and fever), fatigue, recurrent infections, or autoimmune complications. Infection is one of the most important clinical problems in patients with CLL. In a nationwide Danish cohort of all patients diagnosed with CLL between 2010 and 2016 (N = 2905), the cumulative incidence of severe infection, was 31% over 5 years. Autoimmune complications, in most cases, autoimmune thrombocytopenia or haemolytic anaemia, can also present at any time of disease without other signs of CLL progression and occur in approximately 4% to 10% of patients with CLL (Tsang and Parikh 2017; Burger 2020). Patients with CLL are at a higher risk of developing a second primary malignancy (Hisada et al. 2001; Schöllkopf et al. 2007) possibly due to reasons such as perturbed immune function and DNA damage secondary to prior treatment (Benjamini et al. 2015; Bond et al. 2020).

Because CLL is a disease of the elderly, comorbid conditions among patients with CLL are common. Nearly all 400 patients diagnosed with incident CLL (2008 to 2016) in a regional cancer registry in Spain had at least 1 comorbid condition at the time of diagnosis and 29.5% had a high comorbidity score per Charlson Comorbidity Index (Villavicencio et al. 2021). An analysis of 9170 Danish patients with CLL (1997 to 2018) further showed that 35% had at least 1 major comorbidity and 12% had 2 or more major comorbidities (Rotbain et al. 2021). Prevalence of comorbid conditions comes from patients newly diagnosed with CLL in the US (Thurmes et al. 2008; Shanafelt et al. 2016; Strati et al. 2017) and in Denmark (Rotbain et al. 2021).

Several factors may impact the outcome of patients with CLL, including age, stage at diagnosis, specific genetic alterations and elevated levels of Beta-2 microglobulin. Those factors are used in the Chronic Lymphocytic Leukemia International Prognostic Index (CLL-IPI), a valuable tool for assessing the prognosis of patients with CLL. Based on this index, the 5 years survival estimation may vary from approximately 90% for patients at low risk, to approximately 23% for patients with a very high-risk score. At 10 years, the survival expectations may go from approximately 79% to 4% depending on the risk factors identified (Shadman et al, 2023).

## *Management*

Most patients (70%-80%) do not require anti-CLL treatment at the time of diagnosis, and the time to first treatment ranges from months to decades, depending on the clinical and molecular features of the disease (Condoluci et al 2020, Brieghel et al 2022).

Selection of therapy and treatment sequence is guided by clinical factors, biologic and genomic prognostic markers identified at diagnosis, and the prior types of therapies received (Eichhorst et al. 2021; NCCN 2023).

First-line treatment

The treatment landscape for patients with CLL has changed radically over the last 10 years, resulting in markedly improved long-term outcomes (Burger 2020). While chemoimmunotherapy combined with an anti-CD20 antibody had previously formed the foundation of therapy, more recent insights into the biologic dependence of CLL on B-cell receptor signalling as well as anti-apoptotic machinery have led to the successful development of several novel targeted therapies, including agents inhibiting BTK, B-cell lymphoma 2 (Bcl-2), and phosphoinositide 3-kinase delta. The introduction of these novel agents, in particular the covalent BTK inhibitors (ibrutinib, zanubrutinib, and acalabrutinib) and the Bcl-2 inhibitor (venetoclax), have substantially improved the outcome of patients with CLL and have likewise become mainstays of initial therapy, with or without an anti-CD20 antibody, for treatment-naïve patients (Burger et al. 2015; Woyach et al. 2018; Fischer et al. 2019; Shanafelt et al. 2019). In patients with indications for initiating treatment, multiple factors should be considered to select the most appropriate treatment option. The treatment decision should include an assessment of IGHV and del(17p) or TP53 status, as well as patient-related factors such as age, comedication, comorbidities, preferences, drug availability, and potential of treatment adherence (Eichhorst et al. 2021; NCCN 2023).

For patients without del(17p) or TP53 mutation, BTK inhibitor and/or venetoclax-based regimens are included in the most recent version of the NCCN guidelines (Version 3.2023) as preferred treatment options. The same regimens are also recommended in patients with del(17p) or TP53 mutation.

Not all patients are able to receive venetoclax due to comorbid illness or logistical barriers (Seymour et al. 2018; Fischer et al. 2019). In recent real-world data analyses, approximately 80% of patients did not receive a Bcl 2 inhibitor (with or without other agents) following treatment with a BTK inhibitor (Jian et al. 2023; Mato et al. 2023). Key challenges associated with venetoclax include the risk of myelosuppression (especially in patients who received prior chemoimmunotherapy), risk of tumour lysis syndrome and its consequences including renal failure, the need for complex dosing schedules including a ramp-up period, and intense monitoring and sometimes hospitalisation to administer this regimen, which collectively can be prohibitive for some patients.

Relapsed and refractory treatment

The selection of the most appropriate treatment regimen for relapsed/refractory CLL should be based on similar considerations, as previously discussed for the first-line therapy. The type of prior first-line therapy, duration of remission, and acquired resistance to treatment are also important factors to be considered (Eichhorst et al. 2021; NCCN 2023).

Acalabrutinib, ibrutinib, and venetoclax with or without rituximab are approved for the treatment of relapsed/refractory CLL based on the results of Phase 3 randomised studies (ASCEND, RESONATE, and MURANO trials, respectively), and are included in the most recent version of the NCCN guidelines (Version 3.2023) as preferred treatment options for both patients with and without del(17p) or TP53 mutation.

Idelalisib or duvalesib with or without rituximab (Furman et al. 2014; Flinn et al. 2018) have also demonstrated a PFS benefit in a randomised Phase 3 study for patients with relapsed/refractory CLL and are listed in the NCCN guidelines as other recommended regimens regardless of patient's age, comorbidities, and del(17p) or TP53 mutation status. The combinations Fludarabine Cyclophosphamide Rituximab (FCR) or Bendamusitine and Rituximab (BendaR) ± ibrutinib are other therapeutic options that can be considered for patients with relapsed/refractory disease.

Despite major advances in treatment, CLL remains incurable (Lenartova et al. 2016).

### 2.1.2. About the product

Pirtobrutinib (Anatomical Therapeutic Chemical [ATC] code: L01EL05) is a small molecule reversible, non-covalent inhibitor of BTK. BTK is a signalling protein of the BCR and cytokine receptor pathways. In B-cells, BTK signalling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Pirtobrutinib binds to wild-type BTK as well as BTK harbouring C481 mutations leading to inhibition of BTK kinase activity. In non-clinical studies, pirtobrutinib inhibited BTK-mediated B-cell CD69 expression and inhibited malignant B-cell proliferation. Pirtobrutinib showed dose-dependent tumour growth inhibition and induced tumour regression in BTK wild-type and BTK C481S mutant mouse xenograft models.

Pirtobrutinib is indicated for the treatment of adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor.

Orally administered, the drug substance is manufactured as 50 and 100 mg film-coated tablets.

### 2.1.3. General comments on compliance with GCP

All studies in the pirtobrutinib clinical development program are being conducted in accordance with consensus ethics principles derived from international ethics guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation (ICH) Good Clinical Practice Guideline (E6), and applicable laws and regulations

## *2.2. Non-clinical aspects*

No new non-clinical data other than the ERA have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

**Summary of main study results**

| **Substance (INN/Invented Name): pirtobrutinib** | | | |
|---|---|---|---|
| **CAS-number (if available): 2101700-15-4** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD 107 | pH 5 = 2.965<br>pH 7 = 2.850<br>pH 9 = 2.757 | log $K_{ow}$ <4.5<br>No bioaccumulation potential |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation potential - log $K_{ow}$ | OECD 107 | pH 5 = 2.965<br>pH 7 = 2.850<br>pH 9 = 2.757 | not B |
| Persistence | OECD 308<br>$DT_{50}$ at 12°C | Sediments from two different river systems:<br>- $DT_{50}$ water:148.7 d<br><br>- $DT_{50}$ whole system: 40, 393 d | vP |

| | | | | | |
|---|---|---|---|---|---|
| Toxicity | CMR | Toxicity to reproduction observed | | | T |
| **PBT-statement:** | Pirtobrutinib is not considered as PBT nor vPvB | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| PEC $_{surfacewater}$ | 0.074 | µg/L | | | < 0.01 threshold (N) |
| Other concerns (e.g. chemical class) | | | | | (N) |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | Soil:<br>$K_{Foc}$ = 731 L·kg$^{-1}$ (soil 1)<br>$K_{Foc}$ = 720 L·kg$^{-1}$ (soil 2)<br>$K_{Foc}$ = 414 L·kg$^{-1}$ (soil 3)<br>$K_{Foc}$ = 768 L·kg$^{-1}$ (soil 4)<br><br>Sludge:<br>$K_{oc}$ = 114 L·kg$^{-1}$ (sludge 1)<br>$K_{oc}$ = 234 L·kg$^{-1}$ (sludge 2)<br>$K_{oc}$ = 197 L·kg$^{-1}$ (sludge 3) | | | Soil:<br>average $K_{Foc}$ used in ERA, 658 L·kg$^{-1}$ |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50, water}$ = 10.8 d (1), 69.7 d* (2)<br>$DT_{50, sediment}$ = 36.7 d (1), nd (2)<br>$DT_{50, system}$ = 18.7 d (1), 185 d (2)<br>(1) = Tarnock (HOC) sediment,<br>(2) = Ashprington (LOC) sediment<br><br>% shifting to sediment = 25.4/41.6%<br><br>% $CO_2$ = 0.1% (1), 0.6% (2)<br>% NER = 20.5% (1),13.5% (2)<br><br>Transformation products >10% = YES,<br>TP RRT 0.80: RT: 0.79-0.81, HPLC: 12.5 %<br>TP RRT 1.02: RT: 1.01-1.03, HPLC: 47.6 % | | | at 20°C.<br>*DFOP, k2DT50, slow phase.<br>Sediment from two different river systems evaluated.<br>At day 14, (%parent + %NER), Sediment risk assessment triggered<br>At test end<br>At test end<br><br>Water, day 101 (2)<br><br>Sediment, d 101 (1)<br>TP RRT: 0.80: molecular formula: C14H13O3N4F3<br>TP RRT: 1.02: molecular formula: C21H19F4N5O3 |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/ *Raphidocelis subcapitata* | OECD 201 | NOEC | 504 | µg/L | Growth rate and yield |
| *Daphnia* sp. Reproduction Test/*Daphnia magna* | OECD 211 | NOEC | 1760 | µg/L | Reproduction |
| Fish, Early Life Stage Toxicity Test/ *Pimephales promelas* | OECD 210 | NOEC | 9950 | µg/L | Total length, wet weight, dry weight |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC | 1000000 | µg/L | Heterotrophic, nitrification and total respiration |
| ***Phase IIb Studies*** | | | | | |
| Sediment dwelling organism/ *Chironomus riparius* | OECD 218 | NOEC | 31 | mg/kg | 1.7% o.c. content |

| | | | | | |
|---|---|---|---|---|---|
| | | NOEC | 182 | | Emergence ratio, male and female development rate, normalized to 10% organic carbon |

## 2.2.2. Discussion on non-clinical aspects

An ERA was submitted with this application updating where necessary the one submitted with the initial MAA for Jaypirca.

Screening for PBT potential, the OECD 107 study was assessed during the initial MAA. As these log Kow values also were <3, a bioconcentration study in Tier B was not triggered.

The $PEC_{SW}$ calculation was updated with more recent prevalence data for both indications (Globocan 2022 database, published in 2024). For the Fpen refinement, Fpen value is therefore updated with the addition of percent of market penetration calculated in function of the prevalence values of the additional indication CLL and with the updated prevalence of MCL indication.

The $PEC_{Surface\ water}$ for pirtobrutinib was then calculated with that Fpen refined of 0.000103 for MCL and of 0.00064 for CLL) and for a maximum daily dose of 200 mg, resulting in a PEC value of 0.074 $\mu g \cdot L^{-1}$ above the EMA guideline action limit of 0.01 $\mu g \cdot L^{-1}$. The PECSurface water for pirtobrutinib was also above the action limit in the initial ERA (2022) for the MAA. Therefore, a Phase II assessment was also described in this updated ERA. Studies performed in the submitted Phase II tier A and B are the same one than those assessed in the initial assessment during the initial MAA, except that one additional study performed to complete the discussion regarding the assessment of the reprotoxic potential in fish which have been raised during the initial MAA. Of course, the values derived from the updated $PEC_{surface\ water}$ are also revised (PEC sediment, PECGround water, PEC aeration tank) and consequently, the ratio PEC/PNEC (Tier A and B).

The updated ratios PEC/PNEC are still <1. These maximum PEC values are still several orders of magnitude lower than the PNEC values. The risk for the environment remains unchanged with the addition of this new additional indication (CLL). Pirtobrutinib is very persistent in sediment according to the OECD 308 study but is not considered a PBT substance. Pirtobrutinib is not expected to pose a risk to the environment.

## 2.2.3. Conclusion on the non-clinical aspects

In accordance with the current guidelines only an update to the Environmental Risk Assessment (ERA) was submitted. The risk for the environment remains unchanged with the updated ERA and thus pirtobrutinib is not expected to pose a risk to the environment.

# *2.3. Clinical aspects*

## 2.3.1. Introduction

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Type of Study | Study ID | Location of Study Report | Objectives | Study Design | Dosing Regimen | Enrollment | Study Population | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy | LOXO-BTK-18001 | 5.3.5.2 | To evaluate MTD, efficacy, safety, and PK | Open-label, non-randomized study | Monotherapy: Phase 1: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, QD Phase 2: 200 mg, QD Combination Phase 1b: Arm A: pirtobrutinib (200 mg) plus venetoclax (400 mg QD after dose ramp-up) Arm B: pirtobrutinib (200 mg) plus venetoclax (400 mg QD after dose ramp-up) and rituximab (375 mg/m$^2$ first dose, then 500 mg/m$^2$ once per cycle; 6 cycles; total 6 doses) | 778 (monotherapy) 25 (combination therapy) | Patients with histologically confirmed B-cell malignancy | Continuous 28-day cycles | Study ongoing; enrollment complete Interim report |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy | LOXO-BTK-20020[a] | 5.3.5.1 | To evaluate safety and efficacy | Open-label, randomized, cross-over optional study | Arm A: pirtobrutinib (200 mg QD); Arm B: Investigator's choice of idelalisib (150 mg BID) plus rituximab[b] or bendamustine (70 mg/m$^2$ IV) plus rituximab[c] | 238 | Relapsed/ refractory CLL/SLL patients pre-treated with covalent BTK inhibitor | Continuous 28-day cycles | Study conduct ongoing (visit cutoff 29 Aug 2023); Final report |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PK modeling | LOXO-305-DMPK-096 | 5.3.3.5 | To characterize the exposure-response of pirtobrutinib for patients in Study 18001 | Population PK modeling study | N/A | N/A | PK data from patients | N/A | Completed; Final report |
| PK modeling | LOXO-305-DMPK-098 | 5.3.3.5 | To characterize the PK and exposure-response of pirtobrutinib of patients Study 20020 | Population PK modeling study | N/A | N/A | PK data from patients | N/A | Completed; Final report |

## 2.3.2. Pharmacokinetics

The MAH updated their popPK analysis, which was evaluated during the initial MAA for Jaypirca, by including patients from Study 18001 (data cutoff: 08 February 2023) and Study 20020 (data cutoff: 29 August 2023) (LOXO-305-DMPK-098). A total of 780 patients were included in this PK analysis population.

In Study 18001, conducted globally, patients with CLL/SLL and NHL were included. A total of 7 dose levels were explored in the Phase 1 dose escalation, ranging from 25 mg to 300 mg QD. At the end of dose escalation, the recommended Phase 2 dose (RP2D) was determined to be 200 mg QD. Patients in the Phase 1 expansion and Phase 2 received the RP2D starting dose of 200 mg QD. Intra-patient dose escalation was permitted once each dose level was cleared for safety. Intra-patient dose escalation occurred frequently in Phase 1, whereas in Phase 2 it only occurred on occasion if the patient experienced progressive disease and it was agreed that the patient would benefit from continuing on study and/or the Investigator believed that the patient may benefit from continuing on a higher dose of pirtobrutinib. For management of safety and tolerability, dose reductions were permitted. Dose reductions occurred infrequently in Study 18001, with approximately 7.1% of patients who received 200 mg QD as a starting dose experiencing a dose reduction.

Study 20020 is a randomized, open-label study comparing pirtobrutinib (Arm A) to Investigator's choice of either idelalisib plus rituximab or bendamustine plus rituximab (Arm B) in CLL/SLL patients who were treated with at least a covalent BTK inhibitor (BTKi). Patients received 200 mg pirtobrutinib QD starting on Cycle 1 Day 1 (C1D1). The cycle length was 28 days. Individual patients continued pirtobrutinib dosing until progressive disease (PD), unacceptable toxicity, or other reasons for treatment discontinuation. Dose reductions were permitted for tolerability, from 200 mg QD to 100 mg QD, and from 100 mg QD to 50 mg QD as appropriate. Re-escalation from a reduced dose was permitted but could not exceed 200 mg QD. 7.8% of the patients in Study 20020 experienced a dose-reduction.

Baseline patient characteristics of the subjects included in the popPK analysis are summarised in **Table 1**.

**Table 1.** Summary of continuous baseline patient characteristics for the population PK analysis (Study 18001 and Study 20020) and Exposure-Response Analysis (Study 20020)

| | PopPK | | | Exposure-response (Study 20020) | | |
|---|---|---|---|---|---|---|
| | Total (N=780) | Study 20020 (N=112) | Study 18001 (N=668) | Safety Mixed Effects (N=116) | ORR/BOR (N=111) | TTE/PFS (N=102) |
| **Age (years)** | | | | | | |
| range | 22 - 95 | 42 - 85 | 22 - 95 | 42 - 85 | 44 - 85 | 44 - 85 |
| median | 68 | 67 | 68 | 66.5 | 67 | 66 |
| mean (%CV) | 67.3 (14.8) | 66.9 (13.8) | 67.4 (15) | 66.8 (13.7) | 67 (13.5) | 66.8 (13.8) |
| **Weight (kg)**[a] | | | | | | |
| range | 35.7 - 152 | 47.4 - 128 | 35.7 - 152 | 47.4 - 128 | 47.4 - 128 | 47.4 - 128 |
| median | 76.3 | 74.9 | 76.6 | 76 | 74 | 72.2 |
| mean (%CV) | 78.1 (22.1) | 76.9 (21.3) | 78.2 (22.3) | 77.4 (21) | 77 (21.5) | 76.7 (21.5) |
| **Body Mass Index ($kg/m^2$)**[b] | | | | | | |
| range | 14.1 - 47.2 | 18.5 - 43 | 14.1 - 47.2 | 18.5 - 43 | 18.5 - 43 | 18.5 - 43 |
| median | 26.2 | 25.4 | 26.3 | 25.8 | 25.4 | 25.2 |
| mean (%CV) | 26.7 (17.9) | 26.4 (18.1) | 26.7 (17.9) | 26.5 (18) | 26.4 (18.2) | 26.2 (17.9) |
| **Serum Albumin (g/L)**[c] | | | | | | |
| range | 19 - 56.5 | 25 - 53.3 | 19 - 56.5 | 25 - 53.3 | 25 - 53.3 | 25 - 53.3 |
| median | 41 | 42 | 41 | 42 | 42 | 42 |
| mean (%CV) | 40.2 (13.4) | 41.8 (11.7) | 39.9 (13.6) | 41.8 (11.5) | 41.8 (11.6) | 41.8 (11.9) |
| **Absolute eGFR (mL/min)**[d,e] | | | | | | |
| range | 26.2 - 159 | 26.6 - 134 | 26.2 - 159 | 26.6 - 134 | 26.6 - 134 | 26.6 - 134 |
| median | 78 | 75.4 | 78.6 | 75.7 | 75.2 | 75.7 |
| mean (%CV) | 78.9 (30.2) | 74.9 (31.6) | 79.6 (29.9) | 75.4 (31.2) | 74.7 (31.6) | 75.1 (30.7) |

*Note:*

Abbreviations: BOR = best overall response; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; %CV = percent coefficient of variation; eGFR = estimated glomerular filtration rate; N = number of patients; ORR = overall response rate; PFS = progression-free survival; PopPK = population pharmacokinetics; TTE = time-to-event

[a] Baseline body weight missing for 2 patients of Study 18001

[b] Height missing for 35 patients of Study 18001 and 2 patients of Study 20020

[c] Baseline serum albumin missing for 2 patients of Study 20020

[d] Absolute eGFR as calculated by the CKD-EPI: $GFR = 141 \times \min(Scr/\kappa,\ 1)^{\alpha} \times \max(Scr/\kappa,\ 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] or 1.159 [if black], where Scr is serum creatinine, $\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males, min indicates the minimum of $Scr/\kappa$ or 1, and max indicates the maximum of $Scr/\kappa$ or 1. (Levey et al. 2009 [2]).

[e] Absolute eGFR missing for 35 patients of Study 18001 and 2 patients of Study 20020

The structure of the previously developed population PK model was maintained for the current analysis with data-update. Model parameter estimation was performed with overall high precision and interindividual variability was generally low to moderate. Parameter estimates are presented in **Table 2**.

**Table 2**. Parameter estimates of the final population PK model LOXO-305-DMPK-098

| | Final model estimate (% RSE) | 95% CI from bootstrap |
|---|---|---|
| Bioavailability (F, fraction, $\theta 1$) | 1 fixed | 1 fixed |
| Mean Transit Time (MTT, h, $\theta 2$) | 1.06 (1.45) | (0.996, 1.14) |
| Clearance (CL, L/h, $\theta 3$) | 2.05 (1.46) | (1.99, 2.11) |
| Intercompartmental clearance (Q, L/h, $\theta 5$) | 7.74 (8.74) | (5.81, 9.95) |
| Central volume of distribution (Vc, L, $\theta 4$) | 34.2 (2.00) | (31.5, 36.7) |
| Peripheral volume of distribution (Vp, L, $\theta 6$) | 18.5 (4.26) | (16.3, 20.9) |
| **Covariate Effects** | | |
| *Allometry on CL and Q* | | |
| Body Weight (kg, $\theta 9$)[a] | 0.355 (17.4) | (0.219, 0.487) |
| *Allometry on Vc and Vp* | | |
| Body Weight (kg, $\theta 10$)[b] | 0.808 (5.89) | (0.705, 0.905) |
| *Covariate effects on CL* | | |
| eGFR (mL/min, $\theta 12$)[c] | 0.00390 (17.2) | (0.00253, 0.00512) |
| Albumin (g/L, $\theta 11$)[d] | -0.633 (16.1) | (-0.822, -0.448) |
| *Covariate effect on Vc* | | |
| Albumin (g/L, $\theta 13$)[e] | -0.522 (32.5) | (-0.755, -0.321) |
| **Interindividual variability (CV%)** | | |
| MTT (%, $\omega 2$) | 25.1 (14.0) | (16.7, 32.6) |
| CL (%, $\omega 3$) | 35.7 (3.36) | (33.2, 38.2) |
| **Interocassion varibility (CV%)** | | |
| MTT (%) | 48.7 (5.91) | (42.1, 58.2) |
| **Residual variability** | | |
| Proportional | 0.218 (2.16) | (0.208, 0.225) |

Final population PK model parameter estimates study LOXO-305-DMPK-098 - Pirtobrutinib in Patients of Study LOXO-BTK-18001 (BRUIN; J2N-OX-JZNA) and Study LOXO-BTK-20020 (BRUIN-CLL-321; J2N-OX-JZNN). Values are reported as estimate (relative standard error, % RSE). Interindividual variability is reported as % CV and calculated as $100 * \sqrt{\exp(sd^2) - 1}$ [4].

Abbreviations: ALB = serum albumin; CI = coverage interval; CL = clearance; CV = coefficient of variation; F = relative bioavailability; eGFR = absolute estimated glomerular filtration rate; MTT = mean transit time; NA = not applicable; Q = intercompartmental clearance; RSE = relative standar error; Vc = central volume of distribution; Vp = peripheral volume of distribution; WT=body weight at entry.

[a] CL/F = Population estimate of CL*((WT/70)**$\theta 9$); Q/F=Population estimate of Q*(WT/70)**$\theta 9$).

[b] Vc/F = Population estimate of Vc*((WT/70)**$\theta 10$); Vp/F=Population estimate of Vp*((WT/70)**$\theta 10$).

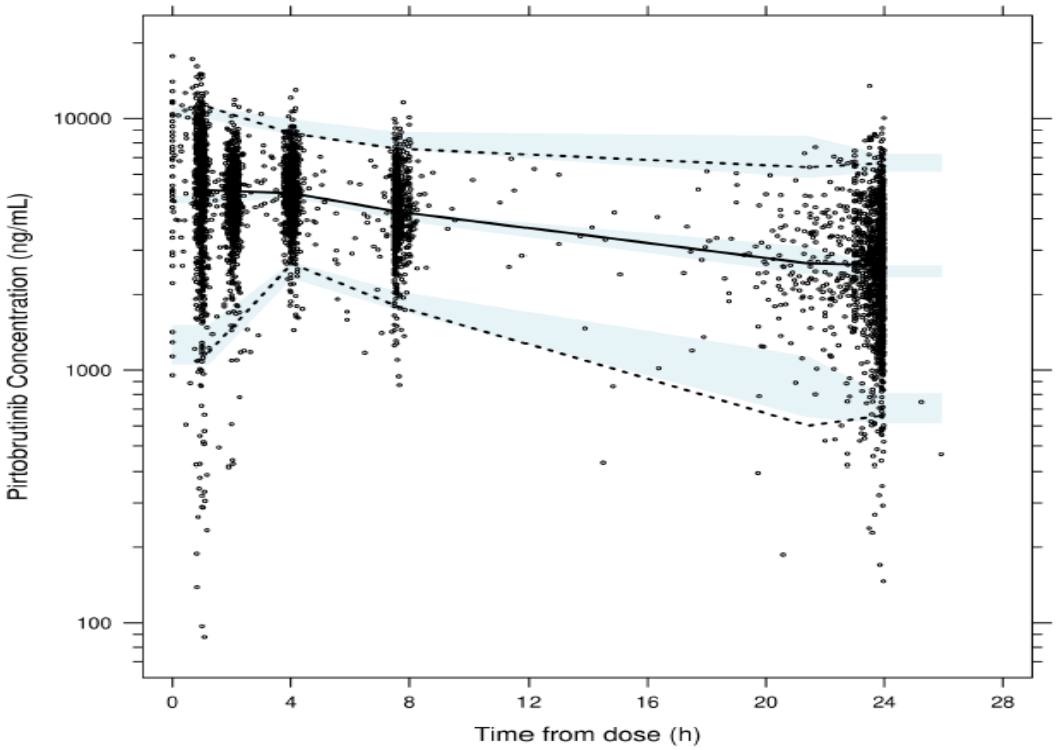
[c] CL/F = Population estimate of CL*(exp($\theta 12$*(eGFR-78.075)).

[d] CL/F = Population estimate of CL*((ALB/41)**$\theta 11$).

[e] Vc/F = Population estimate of Vc*((ALB/41)**$\theta 13$).

Goodness-of-fit and other diagnostic plots indicated adequate fidelity between model predictions and observed data and the absence of overt bias. The Prediction-corrected visual predictive check (pcVPC, **Figure 1**) showed good agreement between observed and model-predicted concentrations with the previously developed popPK model.

**Figure 1.** Prediction-corrected visual predictive check of the population pharmacokinetic model for pirtobrutinib. Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue area depicts the model-predicted 95% confidence interval for 5th, 50th (median), and 95th percentiles.




The PK exposure of patients receiving 200 mg QD was similar between Study 20020 and Study 18001:

• For patients from Study 20020 receiving pirtobrutinib 200 mg QD (N = 112), popPK model-estimated mean Cmax,ss, Cmin,ss, and AUC0-24,ss were 6840 ng/mL (23% CV), 2600 ng/mL (51% CV), and 99800 ng × h/mL (34% CV), respectively.

• For patients from Study 18001 receiving pirtobrutinib 200 mg QD (N = 583), popPK model-estimated mean Cmax,ss, Cmin,ss, and AUC0-24,ss were 6440 ng/mL (26% CV), 2280 ng/mL (62% CV), and 91300 ng × h/mL (39% CV), respectively. Simulation based on combined population of Study 20020 and Study 18001 suggested at 200 mg QD, 97% of patients are predicted to exceed 90% inhibition of BTK, and 66% of patients are predicted to achieve concentrations which exceed 96% inhibition of BTK at steady state, indicating extensive and durable engagement of the drug target.

## 2.3.3. Pharmacodynamics

**Efficacy Exposure-Response Relationships in Patients**

The efficacy exposure-response analysis included patients from Study 20020. Two efficacy endpoints were evaluated in the efficacy exposure-response analysis: progression-free survival (PFS), the primary trial endpoint, and overall response rate (ORR), defined as the proportion of patients who achieve a best overall response (BOR) of complete remission (CR), complete remission with an incomplete marrow recovery (CRi), nodular partial remission (nPR), or partial remission (PR) at or before the initiation of subsequent anticancer therapy. The measures of exposure were the average concentration of pirtobrutinib from the start of treatment up to the time of the event (Cav) and the

trough concentration of pirtobrutinib based on the dose taken just prior to the time of the event (Cmin).

The exposure-response analyses included all patients enrolled in Study 20020 (N=116) who received 1 or more doses of pirtobrutinib monotherapy who had sufficient dosing histories.

**ORR Exposure-Response Analysis**

Final parameter estimates are provided in **Table 3**.

The relationship between average or trough concentration up to the time of the BOR and ORR was not statistically significant. The final logistic regression model VPC is illustrated in **Figure 2** per average pirtobrutinib concentration

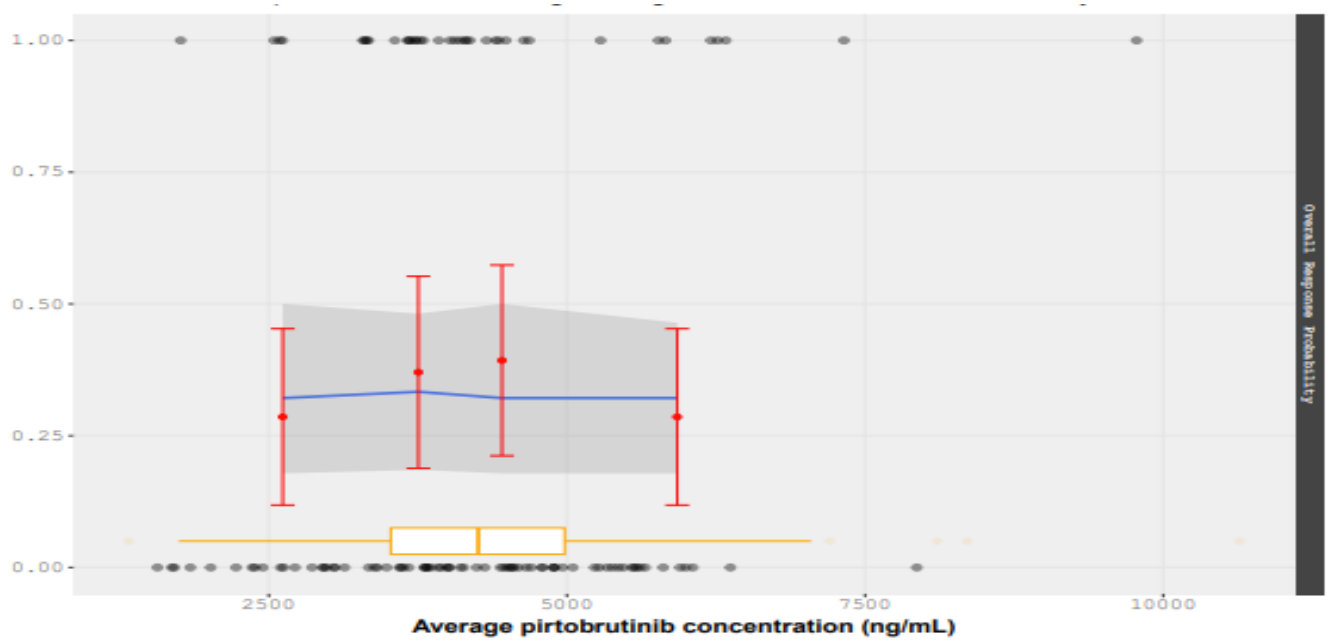
**Table 3**. Parameter Estimates from Logistic Regression Model for ORR

| Parameter Description | Estimate (%RSE) | Probability of ORR |
|---|---|---|
| Parameter for LOGIT | -0.6937 (29.0) | 0.333 |

Values are reported as estimate (relative standard error, %RSE).

Abbreviations: ORR = Overall Response Rate; RSE = relative standard error.

**Figure 2.** Visual predictive check of logistic regression model for ORR.




*Y-axis represents the probability of ORR*

*Abbreviations: CI = confidence interval; ORR = overall response rate. Solid blue lines and gray shaded areas represent the logistic regressions and 95% CIs of the predicted probability of ORR. Grey circles reflect the observed ORR in pirtobrutinib treated patients per the predicted average concentration from start of treatment until time of BOR, taking into account patients' dosing history. The observed response rate (red circle) and 95% CI (red error bars) of each exposure quartile are plotted versus concentration. The yellow box plot represents the 25th, 50th, and 75th percentiles of predicted*

*average steady-state pirtobrutinib concentration for a 200 mg dose in the Study 20020 popPK population (n=112). Whiskers represent 1.5 times the inter-quartile range*

**PFS Exposure-Response Analysis**

Exposure-response was evaluated on the exponential base model with lag-time, as this model required one parameter less. The relationship between average or trough concentration and the baseline hazard was found to be statistically significant. Most profound was the log-linear covariate relationship between the pirtobrutinib trough concentration (Cmin) and baseline hazard (dOFV = -7.2).

**Table 4** gives the parameter estimates and bootstrap results of the final model and **Figure 3** shows the stratified VPC for final TTE model of PFS.

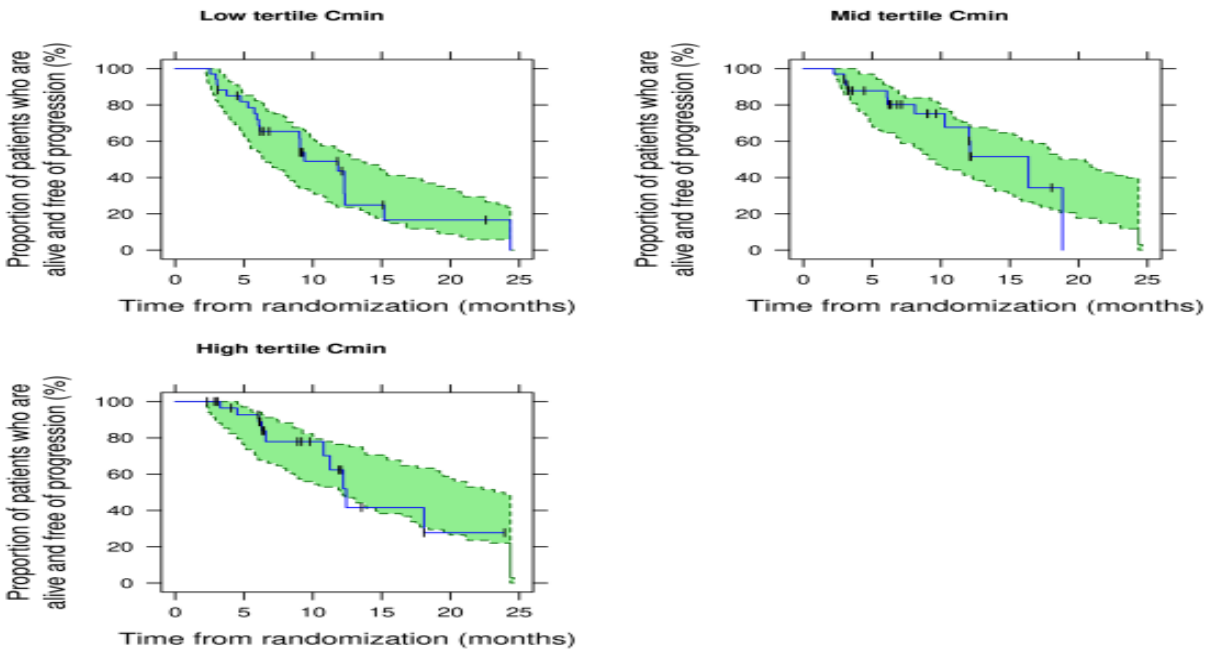
**Table 4**. Parameter Estimates from time to event model for PFS

| Parameter description | Estimate (% RSE) | 95% CI of Bootstrap |
|---|---|---|
| Baseline Hazard | 0.01217 (38.9) | (0.00546, 0.0224) |
| Lag time (days) | 61.93 (0.0) | (61.8, 83.0) |
| **Covariate effect** | | |
| $Log(C_{min})$ on baseline hazard (ng/mL, $\exp(\theta 3)$)[a] | 0.1031 (9.2) | (0.0635, 0.114) |

[a] Baseline hazard = Population estimate of baseline hazard * (1- $\exp(\theta 3)$ * $\log(C_{min})$)

Abbreviations: CI: Confidence Interval, PFS: progression-free survival, RSE: relative standard error, calculated as 100*SE for log-transformed theta's.

**Figure 3.** Visual predictive check TTE model of PFS.




*Y-axis represents the % of patients who are alive and free of progression. The blue line is a Kaplan-Meier plot of the observed data and the green shaded areas represent 95% prediction intervals of the simulated data. Facets display the VPC stratified for the lowest, mid and highest tertile of pirtobrutinib trough concentration at time of event. Abbreviations: PFS = progression free survival; TTE = time-to-event.*

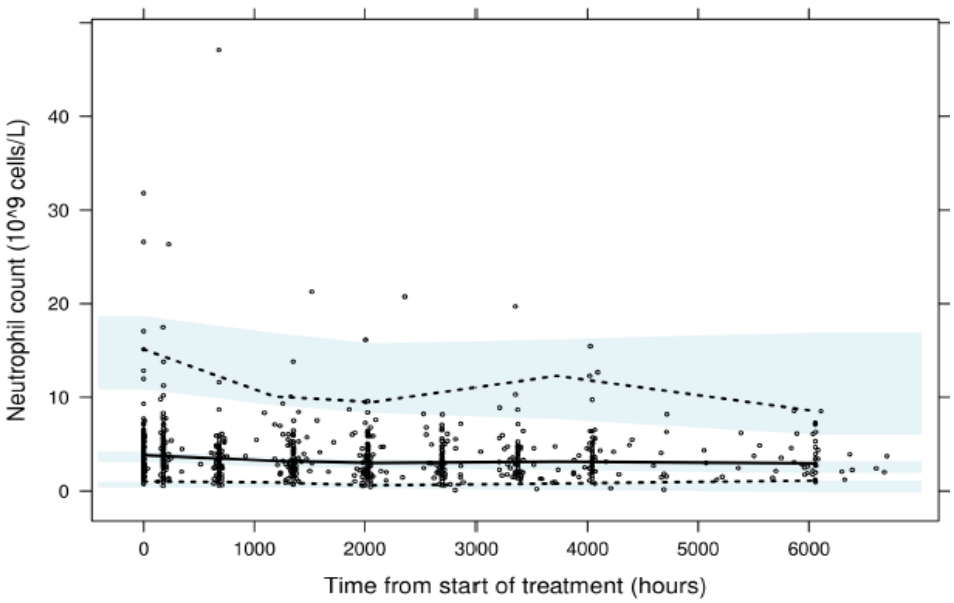
***Safety Exposure-Response Relationships in Patients***

The safety exposure-response analysis included all patients from Study 20020 (data cutoff: 29 August 2023) (LOXO-305-DMPK-098) and consisted of a mixed-effects analysis of 5 continuous safety measures over time: neutrophil count, platelet count, haemoglobin and systolic and diastolic blood pressure. The measures of exposure were the average concentration of pirtobrutinib from the start of treatment up to the time of the safety measurement (Cav) and the maximum concentration of pirtobrutinib based on the dose taken just prior to the time of the safety measurement (Cmax).

A constant baseline model best described the trend over time for systolic blood pressure and diastolic blood pressure. Platelet count, neutrophil count and haemoglobin count over time were best described by a sigmoidal Emax model. Parameter with bootstrap coverage interval of the final models could be estimated with good precision (data not shown).

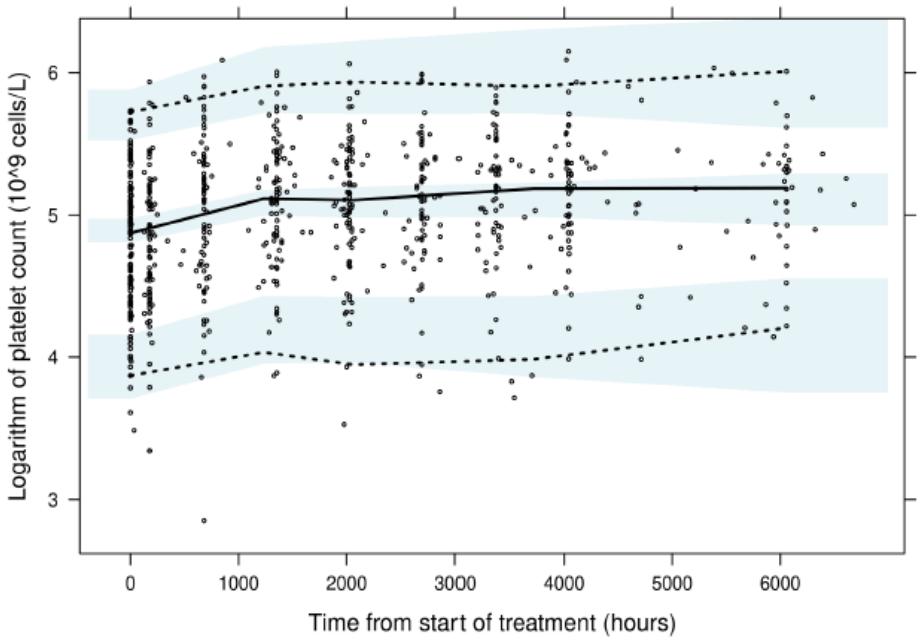
**Figures 4-6** show the VPC of neutrophil count, platelet count and haemoglobin respectively. systolic blood pressure and diastolic blood pressure, respectively. For systolic blood pressure and diastolic blood pressure, no statistically significant relationship was identified between the endpoint and maximum concentration or average concentration (data not shown).

**Figure 4.** Prediction-corrected Visual Predictive Check of neutrophil model



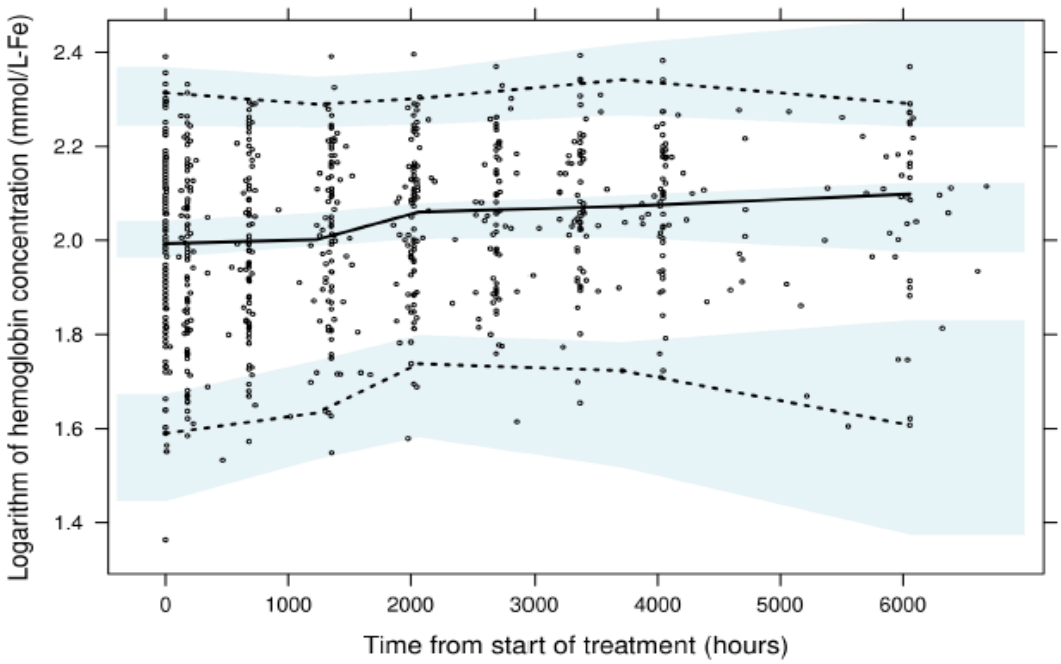

*Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue area depicts the model-predicted 95% confidence interval for 5th, 50th (median), and 95th percentiles.*

**Figure 5.** Prediction-corrected Visual Predictive Check of platelet model




*Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue area depicts the model-predicted 95% confidence interval for 5th, 50th (median), and 95th percentiles.*

**Figure 6.** Prediction-corrected Visual Predictive Check of haemoglobin model




*Solid black line represents median of observed data, dotted black lines represent the 5th and 95th percentiles of observed data. Shaded blue area depicts the model-predicted 95% confidence interval for 5th, 50th (median), and 95th percentiles.*

### 2.3.4. Discussion on clinical pharmacology

The PK of pirtobrutinib in patients with haematological malignancies in the combined population of patients from Study 18001 and Study 20020 was well characterised by a 2-compartment distribution model with linear clearance and 4 transit compartments for absorption. The simulated exposure parameters are consistent with the noncompartmental analysis of the PK in the study population of Study 18001 further demonstrating the ability of the model to describe the observed data.

The covariates from the previous final model (body weight, albumin and eGFR) were retained in the final model. However, as reported in LOXO-305-DMPK-096 Population PK Report, the impact of their inclusion on model-estimated interindividual variability was minimal, so the majority of pirtobrutinib PK variability remains unexplained.

VPC showed a drift toward overestimation of concentrations as compared as to the previous model, but the shrinkage is similar between the two models. At 200 mg QD, BTK inhibition is expected to exceed 96% in the majority of patients (66%) from the combined population of Study 18001 and Study 20020 over the entire dosing interval at steady state.

Regarding efficacy, the model gives reliable estimation. The MAH claims that there is an exposure-response relationship with an increased PFS with increasing exposure (Cmin). However, it is likely that the patients with the lowest Cmin are also patients who had dose adjustments based on tolerability. Thus, the relationship should be interpreted with caution as the relationship could be confounded with the reason for dose adjustment.

The efficacy E-R analyses do not allow a formal conclusion on their own, and the available clinical efficacy outcomes are the pivotal data in this extension of indication application.

The safety E-R analyses showed no increased risk for neutrophil count decrease, or alteration of systolic and diastolic blood pressure, with increased pirtobrutinib exposure. Increased pirtobrutinib exposure was associated with a small increase in haemoglobin level (8.12% increase from the baseline at day 100 for the 95th percentile of Cmax values) which was not considered clinically relevant.

### 2.3.5. Conclusions on clinical pharmacology

The available population PK data and efficacy and safety exposure analyses, support the known PK profile of pirtobrutinib and confirm the proposed starting dose for pirtobrutinib of 200 mg for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton’s tyrosine kinase (BTK) inhibitor.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study

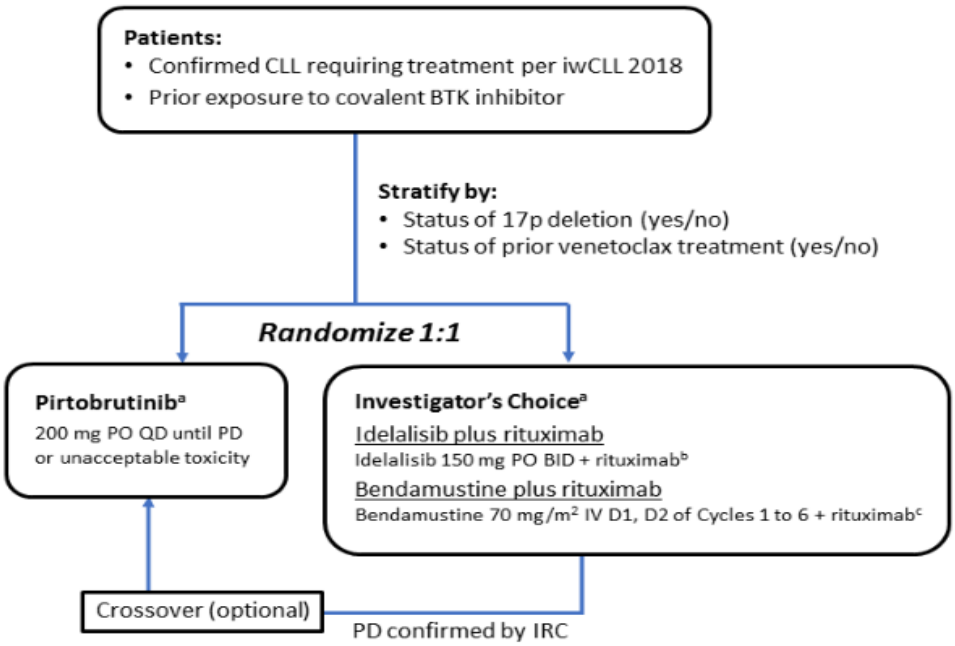
Not applicable.

## 2.4.2. Main study

**Study 20020:** A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-321)

The study design is depicted in **Figure 7**.

**Figure 7.** Study 20020 design




[b] Day 1 of Cycle 1, first dose of rituximab at 375 mg/m², next 4 infusions at 500 mg/m² Q2W, next 3 infusions at 500 mg/m² Q4W.

[c] Day 1 of Cycle 1, first dose of rituximab at 375 mg/m², next 5 infusions Day 1 of Cycle 2 through Cycle 6 at 500 mg/m².

## *Methods*

## Study participants

### Inclusion criteria (selection)

1. Age 18 or older per local regulations at time of enrollment.

2. Confirmed diagnosis by redacted local laboratory report of CLL/SLL as defined by iwCLL 2018 criteria, including the following:

a) B-cells coexpressing the surface antigen CD5 together with at least one B-cell antigen (CD19, CD20, CD23) and either κ or λ light-chain restricted.

b) ≥ 5 × $10^9$ B lymphocytes/L (5000/μL). For SLL patients, history of ≥ 5 × $10^9$ B lymphocytes/L (5000/μL) in the peripheral blood is allowed.

c) Prolymphocytes may comprise ≤ 55% of blood lymphocytes.

3. A requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy such that at least 1 of the following should be met:

a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (such as hemoglobin < 10 g/dL) and/or thrombocytopenia (such as platelets ≤100 × $10^9$/L).

b) Massive (i.e., spleen edge ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly (≥ 13 cm).

c) Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.

d) Progressive lymphocytosis with an increase of > 50% over a 2-month period or lymphocyte doubling time < 6 months. Factors contributing to lymphocytosis other than CLL/SLL (e.g., infections, steroid administration) should be excluded.

e) Autoimmune complications including anaemia or thrombocytopenia poorly responsive to corticosteroids.

f) Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).

g) Disease-related symptoms (also known as B-symptoms) as defined by any of the following:

i) Unintentional weight loss also ≥10% within the previous 6 months

ii) Significant fatigue (i.e., Eastern Cooperative Oncology Group [ECOG] performance scale 2 or worse; cannot work or unable to perform usual activities).

iii) Fevers ≥ 100.5°F or 38.0°C for 2 or more weeks without evidence of infection

iv) Night sweats ≥ 1 month without evidence of infection

4. Known 17p deletion status (wild-type for 17p locus or positive for 17p deletion) by FISH as indicated in Protocol v6.0, Section 1.2.2, Appendix 16.1.1.

5. Previously treated with a covalent BTK inhibitor, investigational or approved, and either alone or in combination with other agents. Patients may have received an unlimited number of lines of prior therapy.

6. Eastern Cooperative Oncology Group (ECOG) 0-2.

7. Must have adequate organ function, as defined in study protocol

8. Patients are required to have had the following washout periods prior to planned C1D1:

a) Targeted agents or cytotoxic chemotherapy: 5 half-lives or 2 weeks, whichever is shorter

b) Anticancer therapeutic monoclonal antibodies: 4 weeks; patients who cross over are not required to observe this washout period prior to starting crossover treatment.

c) Palliative limited field radiation: 7 days

d) Broad field radiation (≥ 30% of bone marrow or whole brain radiotherapy): 28 days

**Exclusion criteria (selection)**

1. Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukaemia, or Hodgkin's lymphoma at any time preceding enrolment.

2. Known or suspected history of central nervous system (CNS) involvement by CLL/SLL.

3. Patients who experienced a major bleeding event on a prior BTK inhibitor.

NOTE: major bleeding was defined as bleeding having one or more of the following features: life-threatening bleeding with signs or symptoms of hemodynamic compromise; bleeding associated with a decrease in the haemoglobin level of at least 2 g/dL; or bleeding in a critical area or organ (e.g. retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome)

4. Active second malignancy; patients with treated second malignancy who are in remission with life expectancy > 2 years and with documented Sponsor approval are eligible. Examples include:

a) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.

b) Adequately treated cervical carcinoma in situ without current evidence of disease.

c) Localized (e.g., lymph node negative) breast cancer treated with curative intent with no evidence of active disease present for more than 3 years and receiving adjuvant hormonal therapy.

d) Localized prostate cancer undergoing active surveillance.

e) History of treated and cured Hodgkin's lymphoma or NHL within 5 years from diagnosis.

5. Major surgery, within 4 weeks of planned start of study treatment.

6. History of ongoing drug-induced pneumonitis.

7. Ongoing drug-induced liver injury, primary biliary cirrhosis and/or extrahepatic obstruction caused by cholelithiasis, and cirrhosis of the liver.

8. History of allogeneic or autologous SCT or CAR-T therapy within the past 60 days.

9 Prior exposure to non-covalent (reversible) BTK inhibitor.

10 Concurrent use of investigational agent or anticancer therapy except hormonal therapy.

**Eligibility criteria for crossover treatment**

Patients who are randomly assigned to Arm B, may be eligible to cross over to Arm A treatment if they meet the following criteria:

a) IRC confirmed PD according to iwCLL 2018

b) Have not received any other anticancer systemic therapy from the time discontinued the control treatment

c) Patients are required to meet inclusion and exclusion criteria to be eligible for crossover to pirtobrutinib, with the exception of Inclusion Criterion 8b (i.e., the washout period described in Inclusion Criterion 8b is not applicable to patients entering crossover treatment). Given the potential for additive risk of serious infection with rituximab and pirtobrutinib, patients should be monitored closely for signs and symptoms of infection.

## Treatments

The study interventions and arm assignments are outlined in **Table 5**.

**Table 5.** Intervention Groups and Duration in Study 20020

| | Arm A | Arm B<br>Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) | | | |
|---|---|---|---|---|---|
| | pirtobrutinib | idelalisib plus rituximab (IdelaR) | | bendamustine plus rituximab (BR) | |
| **Treatment** | pirtobrutinib | idelalisib | rituximab | bendamustine | rituximab |
| **Dose** | 200 mg | 150 mg | 375 mg/m$^2$ on C1D1 and then 500 mg/m$^2$ | 70 mg/m$^2$ | 375 mg/m$^2$ on C1D1 and then 500 mg/m$^2$ |
| **Schedule** | QD in 28-day continuous cycles | BID in 28-day continuous cycles | 375 mg/m$^2$ on C1D1 and then 500 mg/m$^2$ Q2W for 4 infusions and Q4W for 3 infusions | 70 mg/m$^2$ on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6 | 375 mg/m$^2$ on C1D1 and then 500 mg/m$^2$ given on Day 1 of each 28-day cycle, Cycles 2 to 6 |
| **Route** | Oral | Oral | IV | IV | IV |

A cycle was defined as an interval of 28 days during treatment period. The 28-day cycle length was to be maintained throughout the treatment phase regardless of dose interruptions.

Patients began dosing assigned treatment on C1D1 or if crossover, on CO-C1D1. A delay for a maximum of 7 days of a cycle start not due to adverse event, but due to holiday, weekend, bad weather, or other unforeseen circumstances, was permitted and not counted as a protocol deviation. Response assessments were to remain on the original schedule.

## Objectives

Primary objective

- To evaluate PFS of pirtobrutinib as monotherapy (Arm A) compared to Investigator's choice of IdelaR or BendaR (Arm B)

Secondary objectives

- To evaluate the effectiveness of Arm A compared to Arm B
- To evaluate the effectiveness of Arm A compared to Arm B based on patient reported outcomes

Safety objectives

- To evaluate the safety and tolerability of each treatment arm

## Outcomes/endpoints

Primary endpoint

- PFS as assessed by IRC is defined as the time from randomization until the occurrence of documented disease progression by the IRC, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD

Secondary endpoints

- Overall survival (OS) as assessed by Investigator is defined as the time from randomization until death from any cause
- Progression free-survival (PFS) as assessed by Investigator per iwCLL 2018 criteria
- Time to next treatment (TTNT) as assessed by Investigator is defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL
- Event-free survival (EFS) as assessed by Investigator is defined as the time from date of randomization to the date of PD or start of new treatment for CLL or discontinuation from treatment due to toxicity or death, whichever occurs first.
- Overall response rate (ORR) as assessed by Investigator and IRC

  ORR according to IRC-assessed BOR is defined as the number of patients who achieve a best overall response (BOR) of complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR) or PR at or before the initiation of subsequent anticancer therapy divided by the total number of patients randomized to each treatment arm.
- Duration of response (DOR) as assessed by Investigator and IRC is defined as the time from the date of the first documented response until the first date of the documentation of PD per iwCLL 2018 criteria, or the date of death from any cause in the absence of documented PD.

  DoR will be analyzed for patients who achieve a BOR of CR, CRi, nPR or PR. The DoR according to both IRC- and Investigator-assessed BOR will be evaluated.

Patient-reported outcomes (PROs)

- Time to worsening (TTW) of CLL/SLL-related symptoms
- TTW of physical functioning

Safety outcomes

- Including, but not limited to, serious adverse events (SAEs), AEs, deaths and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria in Adverse Events (NCI CTCAE) v5.0.

## Sample size

The sample size of this study was determined (under the assumption of 1:1 randomization) to allow sufficient power for testing IRC-assessed PFS in an error-controlled fashion. For the IRC-assessed PFS, assuming a true HR of 0.5, 88 IRC-assessed PFS events are required to provide approximately 90% power at a 2-sided significance level of 5% to reject the null hypothesis (HR = 1.0) using the logrank test. This corresponds to an improvement in median IRC-assessed PFS from 14.0 months in comparator arm to 28.0 months for pirtobrutinib arm.

Allowing a dropout rate of approximately 10% by the time of primary PFS analysis, the study was expected to enrol approximately 250 patients. The accrual period is assumed to be approximately 12 months, and the final analysis is expected to occur approximately 20 months after the first patient has been randomized.

## Randomisation

All patients were centrally assigned to randomised study treatment using an IXRS. Eligible patients were randomized 1:1 into Arm A or Arm B and were stratified based on presence of deletion 17p (yes/no) and receipt of prior venetoclax treatment (yes/no).

## Blinding (masking)

This was on open-label study.

## Statistical methods

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in the hierarchical order:

1. IRC-assessed PFS, then
2. OS

Since a hierarchical group sequential gate-keeping strategy (Glimm et al. 2010) is used, each hypothesis will be tested at two-sided alpha level of 0.05, and a family-wise type I error will be controlled at two-sided alpha level of 0.05.

Primary endpoints

- Intercurrent-event strategies:
    - Subsequent anticancer therapy for CLL/SLL prior to PD or death without PD is handled with on treatment strategy.
    - Extended time without adequate disease assessment (i.e., 2 or more consecutively missed disease assessment visits) prior to PD or death without PD is handled with on treatment strategy.
- Study intervention discontinuation prior to PD or death without PD is handled with treatment policy strategy
- Population-level summary measure: HR of PFS comparing pirtobrutinib vs IdelaR or BR estimated using a stratified Cox regression model (Cox 1972)

A subsequent anticancer therapy for CLL/SLL taken prior to PD or death without progression will confound the treatment effect of pirtobrutinib in terms of PFS. If the subsequent anticancer therapy is taken, future disease recurrence/progression status is not needed. The participant will be censored and only the time prior to the initiation of the subsequent anticancer therapy will be considered in analysis.

PD or death without progression observed after an extended time without adequate disease assessment may have occurred much earlier but is not reported because the scheduled assessment was not done. This inadequate observation may introduce bias to PFS estimates. If extended time without adequate assessment occurs, the participant will be censored and only the time up to the last adequate tumor assessment will be considered in analysis.

Study intervention discontinuation due to reasons other than PD or death without progression is handled with treatment policy as it reflects clinical practice. Time from randomization until disease

progression, or death without PD, regardless of study intervention discontinuation, will be considered in analysis.

*Sensitivity analyses*

Several sensitivity analyses for the IRC-assessed PFS will be conducted as defined below:

- Repeat the primary analysis for IRC-assessed PFS using unstratified logrank test and an unstratified Cox regression model.
- Subjects with the use of any subsequent anticancer therapy prior to the first IRC confirmed PD or death due to any cause will not be censored at the last adequate assessment prior to the start date of the subsequent anticancer therapy.
- IRC-assessed PD or death after 2 or more consecutively missed visits will be included as a PFS event.
- Exclude patients with IPDs deemed to impact efficacy analysis

Secondary endpoints

- Intercurrent-event strategies:
    - Study intervention discontinuation prior to death is handled with treatment policy strategy.
    - Subsequent anticancer therapy for CLL/SLL (including pirtobrutinib for crossover participants) prior to death is handled with treatment policy strategy.
- Population-level summary measure: Hazard ratio of OS in pirtobrutinib vs IdelaR or BR estimated using a stratified Cox regression model (Cox 1972).

Subgroup analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for the primary efficacy endpoint of PFS assessed by IRC and the key secondary efficacy endpoint of OS will be estimated (with a nominal 95% CI) and plotted using forest plots

Changes to planned analyses

The following changes were made to the protocol-planned analyses: Changes to the timing of OS analyses.

The current SAP is based on version 6.0 of the protocol for Study LOXO-BTK-20020 dated 15 February 2023.

Changes in the planned analyses for the study that were implemented by SAP are described in the Version History in the final version of the SAP. Major changes to the statistical analyses are described below. There were no changes made after the final SAP and before unblinding/database lock.

**Table 6.** Amendments to the SAP for study 20020

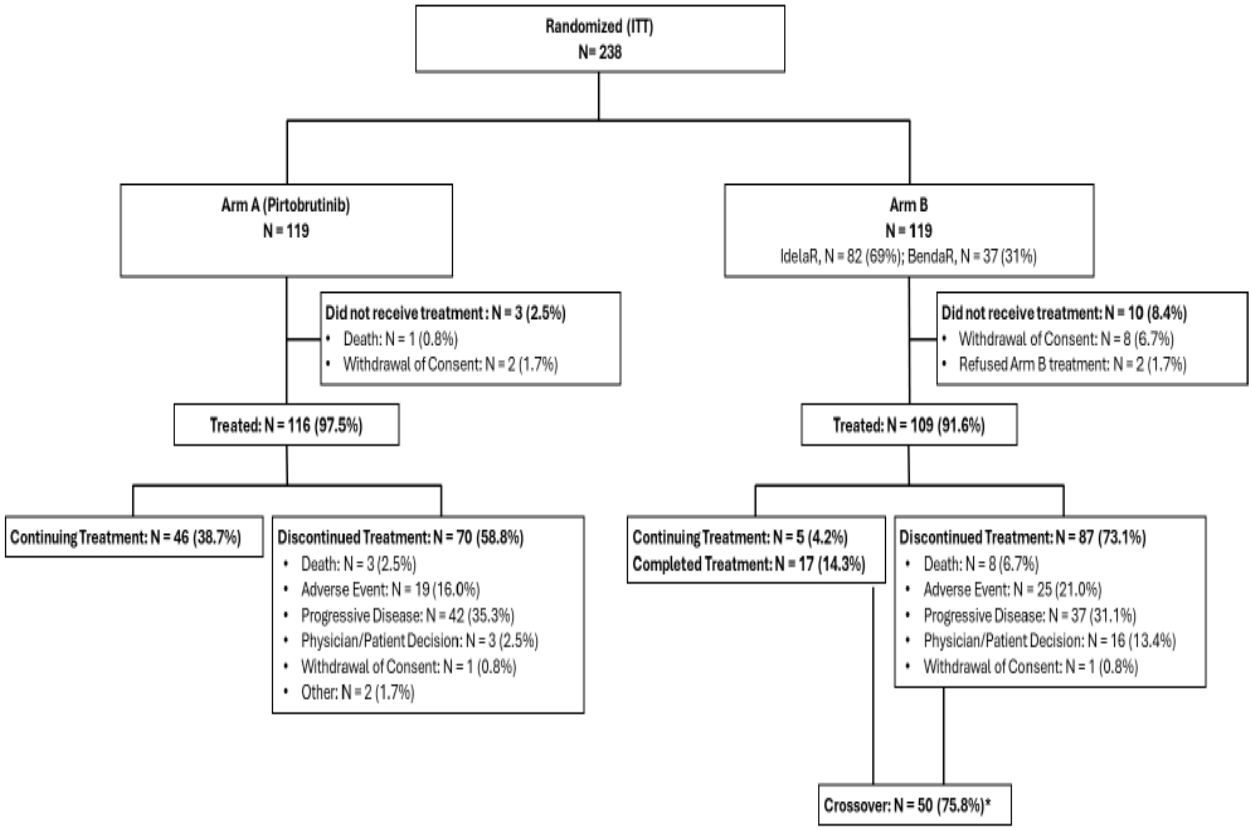
| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1.0 | 11 Jun 2021 | Not applicable | Original version |
| 2.0 | 19 June 2023 | Remove time to treatment failure | Align with the current version of the study protocol |

| | | | |
|---|---|---|---|
| | | Add additional sensitivity analysis to IRC-PFS, OS | Additional sensitivity analysis to evaluate impact of censoring rule and crossover data |
| | | Add subgroup analysis for OS | Add subgroup analysis to better characterize key secondary efficacy endpoint OS |
| | | Update subgroup analysis for Race/Ethnicity | Update to incorporate diversity, equity, and inclusion plan |
| 3.0 | 06 Sep 2023 | Add descriptive interim analysis for OS | Allow data maturity in OS with extended follow-up |
| | | Update in Handling of Missing Data | Align with eCRF data collection and data standard |
| | | Clarification language on sensitivity analysis regarding IPD for IRC-PFS | Align with IPD review process |
| | | Clarification language on subgroup analysis | Provide analysis method for small sample size in subgroups |
| | | Add TTNT censoring rule | Align with other efficacy endpoints |
| | | Miscellaneous revisions | Align with EDC data capture, data standard; minor corrections |

## *Results*

## Participant flow

**Figure 8.** Summary of patient disposition in Study 20020 (DCO: 29 August 2024)




*Among patients whose event was PD and thus had the opportunity to crossover, the effective crossover rate was 75.8% (50/66).

## Recruitment

Study initiation: 09 March 2021 (first patient enrolled).

The study is ongoing.

## Conduct of the study

### Protocol amendments

The first version of the global protocol was issued on 13 October 2020. The key changes to the eligibility criteria are summarized in the table below. First patient was included under global protocol version 3.0.

**Table 7.** Protocol amendments related to eligibility criteria in Study 20020

| Version | Date | Amendments |
|---|---|---|
| 1.0 | 13 October 2020 | Original protocol |
| 2.0 | 03 November 2020 | Revised Criterion 7 to: ≤ 3.0 × the ULN or with documented liver involvement ≤ 5 × ULN (previously was ≤ 2.5 × the ULN)<br><br>Revised Criterion 10 to: Willingness of men and women of reproductive potential to observe conventional and highly effective or acceptable birth control methods for the duration of treatment |

| | | |
|---|---|---|
| | | and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later;<br><br>Revised Criterion 26 to include: Prior toxic epidermal necrolysis with any drug, for patients who are planned to receive idelalisib |
| 3.0 | 07 December 2020 | Revised Criterion 7 to: If an Investigator has chosen bendamustine/rituximab as the Arm B treatment, creatinine clearance must be ≥ (40 mL/minute)<br><br>Revised Criterion 9 to: History of allogeneic or autologous SCT or CAR-T therapy within the past 60 days |
| 4.0 | 06 August 2021 | Revised Criterion 9 to: Prior treatment related AEs must have recovered to Grade ≤ 1, pre-treatment baseline, or are controlled with medications without meeting other exclusion criteria (with the exception of alopecia)<br><br>Revised Criterion 10c to: Documented LVEF by any method of ≤ 40% within the 12 months prior to randomization, unless subsequent measurements (≥ 2 any kind, separated by a minimum of 3 weeks) documents LVEF recovery > 40%<br><br>Revised Criterion 22 to: For patients planned to receive idelalisib: Current treatment with strong CYP3A4 inhibitors or inducers use of idelalisib and during study participation is prohibited: a) grapefruit or products from grapefruit, b) Seville oranges or products from Seville oranges, c) star fruit or products from star fruit. Revised criterion to reflect only those patients receiving idelalisib, because CYP3A inhibitors or inducers are no longer exclusionary for pirtobrutinib; also, CYP1A is not exclusionary by bendamustine label, and this is addressed in the prohibited concomitant medication section |
| 5.0 | 13 September 2022 | Revised Criterion 4 to note known 17p status (wildtype for 17p locus or positive for 17p deletion) is required by FISH<br><br>Revised the table for Criterion 7 to require a lower adequate bone marrow function threshold (ANC, platelets, hemoglobin) for patients with documented bone marrow involvement considered to impair hematopoiesis<br><br>Revised Criterion 22d to prohibit preparations of St. John's Wort<br><br>Revised Criterion 25a to consider allowing patients to receive bendamustine if they have an allergy to idelalisib, and vice versa |
| 6.0 | 15 February 2023 | Revised Criterion 11 to remove text that stated "on at least 2 of 3 consecutive ECGs, and mean QTcF > 470 msec on all 3 ECGs, during Screening." This was based on no observed cardiac safety signals for QTc prolongation with pirtobrutinib |

Important protocol deviations were reported in 21.0% of patients in Arm A and 25.2% in Arm B and are summarised in

**Table 8.** Summary of important protocol deviations (ITT population) in Study 20020

| | Arm A | Arm B | Total |
|---|---|---|---|
| Derivation Type | Pirtobrutinib (N=119) n (%) | IdelaR or BendaR (N=119) n (%) | (N=238) n (%) |
| Number of Patients with at Least One Important Protocol Deviation | 25 ( 21.0) | 30 ( 25.2) | 55 ( 23.1) |
| Study Procedures | 4 ( 3.4) | 18 ( 15.1) | 22 ( 9.2) |
| Visit Schedule | 1 ( 0.8) | 7 ( 5.9) | 8 ( 3.4) |
| Efficacy | 2 ( 1.7) | 3 ( 2.5) | 5 ( 2.1) |
| Laboratory Assessment | 0 | 5 ( 4.2) | 5 ( 2.1) |
| Study Procedures | 0 | 4 ( 3.4) | 4 ( 1.7) |
| Randomization | 1 ( 0.8) | 0 | 1 ( 0.4) |
| Safety | 7 ( 5.9) | 6 ( 5.0) | 13 ( 5.5) |
| Safety | 7 ( 5.9) | 6 ( 5.0) | 13 ( 5.5) |
| Eligibility | 10 ( 8.4) | 2 ( 1.7) | 12 ( 5.0) |
| Inclusion Criteria | 7 ( 5.9) | 1 ( 0.8) | 8 ( 3.4) |
| Exclusion Criteria | 4 ( 3.4) | 1 ( 0.8) | 5 ( 2.1) |
| Informed Consent | 4 ( 3.4) | 5 ( 4.2) | 9 ( 3.8) |
| Informed Consent and Process | 4 ( 3.4) | 5 ( 4.2) | 9 ( 3.8) |
| Investigational Product | 1 ( 0.8) | 1 ( 0.8) | 2 ( 0.8) |
| IP Preparation | 1 ( 0.8) | 0 | 1 ( 0.4) |
| IP Administration | 0 | 1 ( 0.8) | 1 ( 0.4) |
| Concomitant Medication | 1 ( 0.8) | 0 | 1 ( 0.4) |
| Concomitant Medication | 1 ( 0.8) | 0 | 1 ( 0.4) |

Abbreviations:N = number of subjects in population; n = number of subjects in the specified category.

## Baseline data

Demographics and baseline disease characteristics are presented in **Table 9** and **Table 10** respectively.

**Table 9.** Demographics by Study Arm – ITT Population, Study 20020

| | Arm A | Arm B | | | Total |
|---|---|---|---|---|---|
| | Pirtobrutinib (N=119) n (%) | IdelaR or BendaR (N=119) n (%) | IdelaR (N=82) n (%) | BendaR (N=37) n (%) | (N=238) n (%) |
| Sex, n (%) | | | | | |
| Male | 83 ( 69.7) | 83 ( 69.7) | 55 ( 67.1) | 28 ( 75.7) | 166 ( 69.7) |
| Female | 36 ( 30.3) | 36 ( 30.3) | 27 ( 32.9) | 9 ( 24.3) | 72 ( 30.3) |
| Race, n (%) | | | | | |
| Asian | 14 ( 11.8) | 15 ( 12.6) | 1 ( 1.2) | 14 ( 37.8) | 29 ( 12.2) |
| Black or African American | 1 ( 0.8) | 5 ( 4.2) | 3 ( 3.7) | 2 ( 5.4) | 6 ( 2.5) |
| White | 98 ( 82.4) | 95 ( 79.8) | 74 ( 90.2) | 21 ( 56.8) | 193 ( 81.1) |
| Not Reported | 5 ( 4.2) | 4 ( 3.4) | 4 ( 4.9) | 0 | 9 ( 3.8) |
| Unknown | 1 ( 0.8) | 0 | 0 | 0 | 1 ( 0.4) |
| Ethnicity, n (%) | | | | | |
| Hispanic or Latino | 6 ( 5.0) | 4 ( 3.4) | 4 ( 4.9) | 0 | 10 ( 4.2) |
| Not Hispanic or Latino | 107 ( 89.9) | 108 ( 90.8) | 72 ( 87.8) | 36 ( 97.3) | 215 ( 90.3) |
| Not Reported | 4 ( 3.4) | 7 ( 5.9) | 6 ( 7.3) | 1 ( 2.7) | 11 ( 4.6) |
| Unknown | 2 ( 1.7) | 0 | 0 | 0 | 2 ( 0.8) |

| | | | | | |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| n | 119 | 119 | 82 | 37 | 238 |
| Mean (SD) | 66.9 (9.32) | 67.0 (8.52) | 67.9 (8.52) | 65.1 (8.30) | 67.0 (8.91) |
| Median | 66.0 | 68.0 | 68.0 | 66.0 | 67.0 |
| Min - Max | 42.0 - 90.0 | 42.0 - 85.0 | 42.0 - 82.0 | 48.0 - 85.0 | 42.0 - 90.0 |
| **Age Group, n (%)** | | | | | |
| <50 years | 3 ( 2.5) | 4 ( 3.4) | 3 ( 3.7) | 1 ( 2.7) | 7 ( 2.9) |
| >=50 and <65 years | 46 ( 38.7) | 35 ( 29.4) | 20 ( 24.4) | 15 ( 40.5) | 81 ( 34.0) |
| >=65 and <75 years | 41 ( 34.5) | 57 ( 47.9) | 38 ( 46.3) | 19 ( 51.4) | 98 ( 41.2) |
| >=75 and <85 years | 27 ( 22.7) | 22 ( 18.5) | 21 ( 25.6) | 1 ( 2.7) | 49 ( 20.6) |
| >=85 years | 2 ( 1.7) | 1 ( 0.8) | 0 | 1 ( 2.7) | 3 ( 1.3) |
| **Age Group, n (%)** | | | | | |
| <65 years | 49 ( 41.2) | 39 ( 32.8) | 23 ( 28.0) | 16 ( 43.2) | 88 ( 37.0) |
| >=65 years | 70 ( 58.8) | 80 ( 67.2) | 59 ( 72.0) | 21 ( 56.8) | 150 ( 63.0) |
| <75 years | 90 ( 75.6) | 96 ( 80.7) | 61 ( 74.4) | 35 ( 94.6) | 186 ( 78.2) |
| >=75 years | 29 ( 24.4) | 23 ( 19.3) | 21 ( 25.6) | 2 ( 5.4) | 52 ( 21.8) |
| <85 years | 117 ( 98.3) | 118 ( 99.2) | 82 (100.0) | 36 ( 97.3) | 235 ( 98.7) |
| >=85 years | 2 ( 1.7) | 1 ( 0.8) | 0 | 1 ( 2.7) | 3 ( 1.3) |
| **Height (cm)** | | | | | |
| n | 117 | 119 | 82 | 37 | 236 |
| Mean (SD) | 170.07 (9.149) | 171.52 (10.571) | 172.46 (10.928) | 169.43 (9.543) | 170.80 (9.897) |
| Median | 170.00 | 172.00 | 173.00 | 170.00 | 171.00 |
| Min - Max | 151.00 - 190.50 | 148.00 - 198.00 | 148.00 - 198.00 | 149.86 - 190.50 | 148.00 - 198.00 |
| **Weight (kg)** | | | | | |
| n | 119 | 119 | 82 | 37 | 238 |
| Mean (SD) | 77.57 (16.275) | 79.14 (18.098) | 80.67 (18.894) | 75.74 (15.911) | 78.36 (17.192) |
| Median | 76.00 | 76.20 | 79.00 | 72.30 | 76.00 |
| Min - Max | 47.40 - 127.90 | 39.50 - 134.99 | 39.50 - 134.99 | 49.00 - 128.00 | 39.50 - 134.99 |
| **Body Surface Area ($m^2$)** | | | | | |
| n | 117 | 119 | 82 | 37 | 236 |
| Mean (SD) | 1.90 (0.224) | 1.93 (0.257) | 1.96 (0.269) | 1.88 (0.223) | 1.92 (0.241) |
| Median | 1.88 | 1.90 | 1.97 | 1.85 | 1.90 |
| Min - Max | 1.42 - 2.53 | 1.31 - 2.60 | 1.31 - 2.60 | 1.47 - 2.54 | 1.31 - 2.60 |
| **Region, n(%)** | | | | | |
| North America | 24 ( 20.2) | 39 ( 32.8) | 26 ( 31.7) | 13 ( 35.1) | 63 ( 26.5) |
| Europe | 76 ( 63.9) | 63 ( 52.9) | 54 ( 65.9) | 9 ( 24.3) | 139 ( 58.4) |
| Asia | 14 ( 11.8) | 15 ( 12.6) | 1 ( 1.2) | 14 ( 37.8) | 29 ( 12.2) |
| Australia | 5 ( 4.2) | 2 ( 1.7) | 1 ( 1.2) | 1 ( 2.7) | 7 ( 2.9) |

**Table 10.** Baseline Disease Characteristics by Study Arm – ITT Population, Study 20020

| | Arm A | Arm B | | | Total |
|---|---|---|---|---|---|
| | Pirtobrutinib (N=119) n (%) | IdelaR or BendaR (N=119) n (%) | IdelaR (N=82) n (%) | BendaR (N=37) n (%) | Total (N=238) n (%) |
| Duration of Disease (months) * | | | | | |
| n | 119 | 119 | 82 | 37 | 238 |
| Mean (SD) | 123.50 (63.993) | 120.64 (58.578) | 127.19 (56.616) | 106.12 (61.000) | 122.07 (61.233) |
| Median (Q1, Q3) | 118.70 (73.30,170.02) | 120.87 (80.30,154.51) | 123.79 (87.95,161.22) | 98.86 (76.45,141.34) | 119.92 (77.37,161.22) |
| Min - Max | 16.76 - 300.22 | 8.05 - 323.52 | 23.29 - 272.99 | 8.05 - 323.52 | 8.05 - 323.52 |
| Histology | | | | | |
| CLL | 109 ( 91.6) | 108 ( 90.8) | 76 ( 92.7) | 32 ( 86.5) | 217 ( 91.2) |
| SLL | 10 ( 8.4) | 11 ( 9.2) | 6 ( 7.3) | 5 ( 13.5) | 21 ( 8.8) |
| ECOG PS | | | | | |
| 0 | 51 ( 42.9) | 50 ( 42.0) | 34 ( 41.5) | 16 ( 43.2) | 101 ( 42.4) |
| 1 | 56 ( 47.1) | 64 ( 53.8) | 43 ( 52.4) | 21 ( 56.8) | 120 ( 50.4) |
| 2 | 12 ( 10.1) | 5 ( 4.2) | 5 ( 6.1) | 0 | 17 ( 7.1) |
| Rai Stage | | | | | |
| Stage 0 | 7 ( 5.9) | 8 ( 6.7) | 7 ( 8.5) | 1 ( 2.7) | 15 ( 6.3) |
| Stage I | 22 ( 18.5) | 25 ( 21.0) | 17 ( 20.7) | 8 ( 21.6) | 47 ( 19.7) |
| Stage II | 33 ( 27.7) | 27 ( 22.7) | 20 ( 24.4) | 7 ( 18.9) | 60 ( 25.2) |
| Stage III | 8 ( 6.7) | 21 ( 17.6) | 16 ( 19.5) | 5 ( 13.5) | 29 ( 12.2) |
| Stage IV | 43 ( 36.1) | 32 ( 26.9) | 17 ( 20.7) | 15 ( 40.5) | 75 ( 31.5) |
| Missing | 6 ( 5.0) | 6 ( 5.0) | 5 ( 6.1) | 1 ( 2.7) | 12 ( 5.0) |
| Bulky Disease | | | | | |
| Patients with measurable target lesion (lymphnode) | 115 ( 96.6) | 112 ( 94.1) | 78 ( 95.1) | 34 ( 91.9) | 227 ( 95.4) |
| <5cm | 67 ( 56.3) | 54 ( 45.4) | 35 ( 42.7) | 19 ( 51.4) | 121 ( 50.8) |
| >=5cm | 48 ( 40.3) | 58 ( 48.7) | 43 ( 52.4) | 15 ( 40.5) | 106 ( 44.5) |
| <10cm | 100 ( 84.0) | 93 ( 78.2) | 65 ( 79.3) | 28 ( 75.7) | 193 ( 81.1) |
| >=10cm | 15 ( 12.6) | 19 ( 16.0) | 13 ( 15.9) | 6 ( 16.2) | 34 ( 14.3) |
| No measurable target lesion at baseline | 4 ( 3.4) | 7 ( 5.9) | 4 ( 4.9) | 3 ( 8.1) | 11 ( 4.6) |
| Missing | 0 | 0 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| B2 Microglobulin (mg/L) at Baseline, n (%) | | | | | |
| <= 3.5 | 27 ( 22.7) | 39 ( 32.8) | 27 ( 32.9) | 12 ( 32.4) | 66 ( 27.7) |
| > 3.5 | 89 ( 74.8) | 77 ( 64.7) | 53 ( 64.6) | 24 ( 64.9) | 166 ( 69.7) |
| Missing/Unknown | 3 ( 2.5) | 3 ( 2.5) | 2 ( 2.4) | 1 ( 2.7) | 6 ( 2.5) |
| Cytogenetic features (FISH panel, Biomarker Laboratory), n (%) | | | | | |
| 17p Deletion Presence | | | | | |
| Yes | 39 ( 32.8) | 43 ( 36.1) | 34 ( 41.5) | 9 ( 24.3) | 82 ( 34.5) |
| No | 72 ( 60.5) | 69 ( 58.0) | 43 ( 52.4) | 26 ( 70.3) | 141 ( 59.2) |
| Missing/Unknown | 8 ( 6.7) | 7 ( 5.9) | 5 ( 6.1) | 2 ( 5.4) | 15 ( 6.3) |
| 11q Deletion Presence | | | | | |
| Yes | 19 ( 16.0) | 25 ( 21.0) | 15 ( 18.3) | 10 ( 27.0) | 44 ( 18.5) |
| No | 82 ( 68.9) | 74 ( 62.2) | 62 ( 75.6) | 12 ( 32.4) | 156 ( 65.5) |
| Missing/Unknown | 18 ( 15.1) | 20 ( 16.8) | 5 ( 6.1) | 15 ( 40.5) | 38 ( 16.0) |
| High-Risk Features (Biomarker Central Laboratory), n (%) | | | | | |
| IGHV Mutation Status | | | | | |
| Mutated | 7 ( 5.9) | 19 ( 16.0) | 13 ( 15.9) | 6 ( 16.2) | 26 ( 10.9) |
| Unmutated | 90 ( 75.6) | 74 ( 62.2) | 59 ( 72.0) | 15 ( 40.5) | 164 ( 68.9) |
| Missing/Unknown | 22 ( 18.5) | 26 ( 21.8) | 10 ( 12.2) | 16 ( 43.2) | 48 ( 20.2) |
| Complex Karyotype | | | | | |
| Yes | 53 ( 44.5) | 44 ( 37.0) | 36 ( 43.9) | 8 ( 21.6) | 97 ( 40.8) |
| No | 21 ( 17.6) | 31 ( 26.1) | 20 ( 24.4) | 11 ( 29.7) | 52 ( 21.8) |
| Missing/Unknown | 45 ( 37.8) | 44 ( 37.0) | 26 ( 31.7) | 18 ( 48.6) | 89 ( 37.4) |
| TP53 Mutation Status | | | | | |
| Yes | 33 ( 27.7) | 26 ( 21.8) | 23 ( 28.0) | 3 ( 8.1) | 59 ( 24.8) |
| No | 55 ( 46.2) | 55 ( 46.2) | 40 ( 48.8) | 15 ( 40.5) | 110 ( 46.2) |
| Missing/Unknown | 31 ( 26.1) | 38 ( 31.9) | 19 ( 23.2) | 19 ( 51.4) | 69 ( 29.0) |
| TP53 mutation and/or del17p | | | | | |
| Yes | 50 ( 42.0) | 51 ( 42.9) | 40 ( 48.8) | 11 ( 29.7) | 101 ( 42.4) |
| No | 38 ( 31.9) | 37 ( 31.1) | 27 ( 32.9) | 10 ( 27.0) | 75 ( 31.5) |
| Missing/Unknown | 31 ( 26.1) | 31 ( 26.1) | 15 ( 18.3) | 16 ( 43.2) | 62 ( 26.1) |
| TP53 mutation and del17p | | | | | |
| Yes | 22 ( 18.5) | 18 ( 15.1) | 17 ( 20.7) | 1 ( 2.7) | 40 ( 16.8) |
| No | 89 ( 74.8) | 87 ( 73.1) | 56 ( 68.3) | 31 ( 83.8) | 176 ( 73.9) |
| Missing/Unknown | 8 ( 6.7) | 14 ( 11.8) | 9 ( 11.0) | 5 ( 13.5) | 22 ( 9.2) |
| TP53 mutation without 17p deletion | | | | | |
| Yes | 10 ( 8.4) | 7 ( 5.9) | 5 ( 6.1) | 2 ( 5.4) | 17 ( 7.1) |
| No | 77 ( 64.7) | 73 ( 61.3) | 57 ( 69.5) | 16 ( 43.2) | 150 ( 63.0) |
| Missing/Unknown | 32 ( 26.9) | 39 ( 32.8) | 20 ( 24.4) | 19 ( 51.4) | 71 ( 29.8) |
| TP53 mutation, del17p, or unmutated IGHV | | | | | |
| Yes | 93 ( 78.2) | 84 ( 70.6) | 64 ( 78.0) | 20 ( 54.1) | 177 ( 74.4) |
| No | 5 ( 4.2) | 9 ( 7.6) | 5 ( 6.1) | 4 ( 10.8) | 14 ( 5.9) |
| Missing/Unknown | 21 ( 17.6) | 26 ( 21.8) | 13 ( 15.9) | 13 ( 35.1) | 47 ( 19.7) |
| Cytopenia at Baseline | | | | | |
| Neutropenia - absolute neutrophil count (ANC) < 1.5 x $10^9$/L | 11 ( 9.2) | 10 ( 8.4) | 5 ( 6.1) | 5 ( 13.5) | 21 ( 8.8) |
| Anemia - Hgb <11 g/dL | 33 ( 27.7) | 30 ( 25.2) | 23 ( 28.0) | 7 ( 18.9) | 63 ( 26.5) |
| Thrombocytopenia - platelet counts < 100 x $10^9$/L | 42 ( 35.3) | 37 ( 31.1) | 28 ( 34.1) | 9 ( 24.3) | 79 ( 33.2) |
| Any of the above | 62 ( 52.1) | 55 ( 46.2) | 39 ( 47.6) | 16 ( 43.2) | 117 ( 49.2) |
| Disease Related Symptoms | | | | | |
| Weight loss | 9 ( 7.6) | 14 ( 11.8) | 11 ( 13.4) | 3 ( 8.1) | 23 ( 9.7) |
| Fever | 6 ( 5.0) | 3 ( 2.5) | 2 ( 2.4) | 1 ( 2.7) | 9 ( 3.8) |
| Night sweats | 24 ( 20.2) | 25 ( 21.0) | 18 ( 22.0) | 7 ( 18.9) | 49 ( 20.6) |
| Fatigue | 15 ( 12.6) | 15 ( 12.6) | 11 ( 13.4) | 4 ( 10.8) | 30 ( 12.6) |
| Any of the above | 39 ( 32.8) | 36 ( 30.3) | 26 ( 31.7) | 10 ( 27.0) | 75 ( 31.5) |

* Duration of disease (months): (randomisation date - diagnosis of cancer date + 1)/30.4375.

Prior cancer treatment

Prior cancer treatment is presented in **Table 11**.

**Table 11.** Prior Cancer Treatment by Study Arm – ITT Population. Study 20020

| | Arm A | Arm B | | |
|---|---|---|---|---|
| | Pirtobrutinib (N=119) n(%) | IdelaR or BendaR (N=119) n(%) | IdelaR (N=82) n(%) | BendaR (N=37) n(%) |
| Prior Systemic Therapies, n (%) | | | | |
| Prior Covalent BTKi | 119 ( 100) | 119 ( 100) | 82 ( 100) | 37 ( 100) |
| Acalabrutinib | 17 ( 14.3) | 20 ( 16.8) | 14 ( 17.1) | 6 ( 16.2) |
| Ibrutinib | 100 ( 84.0) | 106 ( 89.1) | 74 ( 90.2) | 32 ( 86.5) |
| Zanubrutinib | 9 ( 7.6) | 7 ( 5.9) | 2 ( 2.4) | 5 ( 13.5) |
| Other | 5 ( 4.2) | 3 ( 2.5) | 1 ( 1.2) | 2 ( 5.4) |
| Prior Venetoclax | 60 ( 50.4) | 60 ( 50.4) | 48 ( 58.5) | 12 ( 32.4) |
| Prior BCL2 inhibitor | 60 ( 50.4) | 62 ( 52.1) | 48 ( 58.5) | 14 ( 37.8) |
| Prior Chemotherapy | 81 ( 68.1) | 83 ( 69.7) | 58 ( 70.7) | 25 ( 67.6) |
| Prior Anti-CD20 Antibody | 86 ( 72.3) | 83 ( 69.7) | 59 ( 72.0) | 24 ( 64.9) |
| Prior PI3K Agent | 11 ( 9.2) | 11 ( 9.2) | 3 ( 3.7) | 8 ( 21.6) |
| Prior IMID/Immunomodulator | 2 ( 1.7) | 3 ( 2.5) | 2 ( 2.4) | 1 ( 2.7) |
| Prior Stem Cell Transplant Therapy | 3 ( 2.5) | 1 ( 0.8) | 1 ( 1.2) | 0 |
| Auto-SCT | 1 ( 0.8) | 0 | 0 | 0 |
| Allo-SCT | 2 ( 1.7) | 1 ( 0.8) | 1 ( 1.2) | 0 |
| Prior Other Systemic Therapy | 6 ( 5.0) | 9 ( 7.6) | 5 ( 6.1) | 4 ( 10.8) |
| Prior Other Molecular Pathways/small molecule inhibitors | 6 ( 5.0) | 3 ( 2.5) | 2 ( 2.4) | 1 ( 2.7) |
| Prior Other Immuno-therapies excluding antiCD20 | 0 | 5 ( 4.2) | 3 ( 3.7) | 2 ( 5.4) |
| Number of Lines of Prior Systemic Therapy | | | | |
| n | 119 | 119 | 82 | 37 |
| Mean (SD) | 3.1 ( 1.87) | 3.4 ( 2.23) | 3.4 ( 2.25) | 3.2 ( 2.20) |
| Median | 3.0 | 3.0 | 3.0 | 3.0 |
| Q1, Q3 | 2.0, 4.0 | 2.0, 5.0 | 2.0, 5.0 | 1.0, 4.0 |
| Min, Max | 1.0, 13.0 | 1.0, 11.0 | 1.0, 11.0 | 1.0, 9.0 |
| 1 | 21 ( 17.6) | 28 ( 23.5) | 18 ( 22.0) | 10 ( 27.0) |
| 2 | 30 ( 25.2) | 24 ( 20.2) | 16 ( 19.5) | 8 ( 21.6) |
| 3 | 29 ( 24.4) | 18 ( 15.1) | 13 ( 15.9) | 5 ( 13.5) |
| >=4 | 39 ( 32.8) | 49 ( 41.2) | 35 ( 42.7) | 14 ( 37.8) |
| Number of Lines Where Prior Covalent BTK Inhibitor Was Used | | | | |
| n | 119 | 119 | 82 | 37 |
| Mean (SD) | 1.2 ( 0.41) | 1.2 ( 0.49) | 1.2 ( 0.47) | 1.2 ( 0.53) |
| Median | 1.0 | 1.0 | 1.0 | 1.0 |
| Q1, Q3 | 1.0, 1.0 | 1.0, 1.0 | 1.0, 1.0 | 1.0, 1.0 |
| Min, Max | 1.0, 3.0 | 1.0, 3.0 | 1.0, 3.0 | 1.0, 3.0 |
| 1 | 102 ( 85.7) | 101 ( 84.9) | 70 ( 85.4) | 31 ( 83.8) |
| 2 | 15 ( 12.6) | 13 ( 10.9) | 9 ( 11.0) | 4 ( 10.8) |
| 3 | 2 ( 1.7) | 5 ( 4.2) | 3 ( 3.7) | 2 ( 5.4) |
| Number of Lines Where Prior Venetoclax Was Used | | | | |
| n | 119 | 119 | 82 | 37 |
| Mean (SD) | 0.6 ( 0.62) | 0.6 ( 0.61) | 0.6 ( 0.58) | 0.4 ( 0.64) |
| Median | 1.0 | 1.0 | 1.0 | 0.0 |
| Q1, Q3 | 0.0, 1.0 | 0.0, 1.0 | 0.0, 1.0 | 0.0, 1.0 |
| Min, Max | 0.0, 2.0 | 0.0, 2.0 | 0.0, 2.0 | 0.0, 2.0 |
| 0 | 59 ( 49.6) | 59 ( 49.6) | 34 ( 41.5) | 25 ( 67.6) |
| 1 | 52 ( 43.7) | 53 ( 44.5) | 44 ( 53.7) | 9 ( 24.3) |
| 2 | 8 ( 6.7) | 7 ( 5.9) | 4 ( 4.9) | 3 ( 8.1) |
| Number of Lines of Prior BCL2 | | | | |
| n | 119 | 119 | 82 | 37 |
| Mean (SD) | 0.6 ( 0.62) | 0.6 ( 0.60) | 0.6 ( 0.58) | 0.5 ( 0.65) |
| Median | 1.0 | 1.0 | 1.0 | 0.0 |
| Q1, Q3 | 0.0, 1.0 | 0.0, 1.0 | 0.0, 1.0 | 0.0, 1.0 |
| Min, Max | 0.0, 2.0 | 0.0, 2.0 | 0.0, 2.0 | 0.0, 2.0 |
| 0 | 59 ( 49.6) | 57 ( 47.9) | 34 ( 41.5) | 23 ( 62.2) |
| 1 | 52 ( 43.7) | 55 ( 46.2) | 44 ( 53.7) | 11 ( 29.7) |
| 2 | 8 ( 6.7) | 7 ( 5.9) | 4 ( 4.9) | 3 ( 8.1) |
| Reason for Discontinuation from the Most Recent Covalent BTK Inhibitor, n (%)*a | | | | |
| Disease Progression | 81 ( 68.1) | 85 ( 71.4) | 61 ( 74.4) | 24 ( 64.9) |
| Toxicity | 16 ( 13.4) | 18 ( 15.1) | 11 ( 13.4) | 7 ( 18.9) |
| Other Reason for Discontinuation | 22 ( 18.5) | 13 ( 10.9) | 9 ( 11.0) | 4 ( 10.8) |
| Missing | 0 | 3 ( 2.5) | 1 ( 1.2) | 2 ( 5.4) |

| | | | | |
|---|---|---|---|---|
| Reason for Discontinuation from Any Prior Covalent BTK Inhibitor, n (%)*a | | | | |
| Disease Progression | 83 ( 69.7) | 86 ( 72.3) | 61 ( 74.4) | 25 ( 67.6) |
| Toxicity | 17 ( 14.3) | 19 ( 16.0) | 12 ( 14.6) | 7 ( 18.9) |
| Other Reason for Discontinuation | 19 ( 16.0) | 12 ( 10.1) | 8 ( 9.8) | 4 ( 10.8) |
| Missing | 0 | 2 ( 1.7) | 1 ( 1.2) | 1 ( 2.7) |
| Intolerance to Any Prior Covalent BTK Inhibitor, n (%)*b | | | | |
| Yes | 20 ( 16.8) | 26 ( 21.8) | 17 ( 20.7) | 9 ( 24.3) |
| No | 99 ( 83.2) | 91 ( 76.5) | 64 ( 78.0) | 27 ( 73.0) |
| Missing | 0 | 2 ( 1.7) | 1 ( 1.2) | 1 ( 2.7) |
| Relapsed/Refractory to Most Recent Prior Covalent BTK Inhibitor, n (%)*c | | | | |
| Yes | 104 ( 87.4) | 107 ( 89.9) | 77 ( 93.9) | 30 ( 81.1) |
| No | 15 ( 12.6) | 12 ( 10.1) | 5 ( 6.1) | 7 ( 18.9) |
| Relapsed/Refractory to Any Prior Covalent BTK Inhibitor, n (%)*c | | | | |
| Yes | 105 ( 88.2) | 108 ( 90.8) | 77 ( 93.9) | 31 ( 83.8) |
| No | 14 ( 11.8) | 11 ( 9.2) | 5 ( 6.1) | 6 ( 16.2) |
| Reason for Discontinuation from the Most Recent Venetoclax, n (%)*d | | | | |
| Disease Progression | 35 ( 29.4) | 43 ( 36.1) | 35 ( 42.7) | 8 ( 21.6) |
| Toxicity | 1 ( 0.8) | 4 ( 3.4) | 3 ( 3.7) | 1 ( 2.7) |
| Patient Choice | 1 ( 0.8) | 0 | 0 | 0 |
| Other Reason for Discontinuation | 8 ( 6.7) | 6 ( 5.0) | 5 ( 6.1) | 1 ( 2.7) |
| Reason for Discontinuation from Any Prior Venetoclax, n (%)*d | | | | |
| Disease Progression | 36 ( 30.3) | 43 ( 36.1) | 35 ( 42.7) | 8 ( 21.6) |
| Toxicity | 1 ( 0.8) | 4 ( 3.4) | 3 ( 3.7) | 1 ( 2.7) |
| Patient Choice | 1 ( 0.8) | 0 | 0 | 0 |
| Other Reason for Discontinuation | 7 ( 5.9) | 6 ( 5.0) | 5 ( 6.1) | 1 ( 2.7) |
| Prior Radiotherapy, n (%) | | | | |
| Yes | 2 ( 1.7) | 4 ( 3.4) | 3 ( 3.7) | 1 ( 2.7) |
| No | 117 ( 98.3) | 115 ( 96.6) | 79 ( 96.3) | 36 ( 97.3) |

*a- "Disease Progression" is selected if "PD" for prior covalent BTKi ; otherwise "Toxicity" is selected if toxicity from prior covalent BTKi; otherwise "Other".
*b- Intolerance to prior covalent BTK inhibitor is selected if the reason for discontinuation to prior covalent BTK inhibitor is "Toxicity".
*c- Relapsed/Refractory to prior covalent BTK inhibitor is selected if either the reason for discontinuation of prior covalent BTK inhibitor is "Progression" or there was documented disease progression on or after the covalent BTK-inhibitor containing regimen.
*d- "Disease Progression" is selected if "PD" for prior venetoclax; otherwise "Toxicity" is selected if toxicity from prior Venetoclax, otherwise "Patient Choice" is selected if the patient decided to discontinue from prior venetoclax; otherwise "Other".

Crossover population

For patients in crossover, the baseline characteristics were largely comparable between the 50 patients that crossed over and 69 patients who did not crossover from Arm B. The median age for crossover patients was 69.5 (range, 44-82), while for non- crossover patient, the median age was 66 (range, 42-85).

Patients in both crossover and non-crossover groups had a median of 3 prior lines of therapy (range, 1-11), with all patients having received previous cBTKi treatment. Specifically, 44% of crossover patients and 55.1% of non-crossover patients had received prior venetoclax. Patients from the crossover group exhibited a higher percentage of high-risk features compared to the non-crossover group: unmutated IGHV (80% vs. 49.3%), complex karyotype (46% vs. 30.4%), and del 17(p) (48% vs. 27.5%). The primary reasons for discontinuation of prior cBTKi were disease progression (76% vs. 69.6%) and toxicity (20% vs. 15.9%).

Dose modifications

Dose modifications are summarized as dose reductions, dose holds, dose delays, and infusion interruptions, as shown in **Table 12**.

**Table 12**. Dose Modification by Study Treatment – Safety Population, Study 20020 (DCO: 29 August 2024)

| | Arm A | | Arm B | |
|---|---|---|---|---|
| | Pirtobrutinib (N=116) n (%) | IdelaR or BendaR (N=109) n (%) | IdelaR (N=77) n (%) | BendaR (N=32) n (%) |
| Patients with at least one Dose Modification n(%) | 82 ( 70.7) | 81 ( 74.3) | 63 ( 81.8) | 18 ( 56.3) |
| Number of Patients with Dose Reduction | 13 ( 11.2) | 40 ( 36.7) | 34 ( 44.2) | 6 ( 18.8) |
| Primary Reason for Dose Reduction | | | | |
| Subject Error | 3 ( 2.6) | 6 ( 5.5) | 6 ( 7.8) | 0 |
| Procedure | 0 | 0 | 0 | 0 |
| Adverse Event | 11 ( 9.5) | 30 ( 27.5) | 26 ( 33.8) | 4 ( 12.5) |
| Adverse Event Resolution | 0 | 0 | 0 | 0 |
| Other | 0 | 13 ( 11.9) | 10 ( 13.0) | 3 ( 9.4) |
| Number of Patients with Dose Hold | 79 ( 68.1) | 57 ( 52.3) | 57 ( 74.0) | -- |
| Primary Reason for Dose Hold | | | | |
| Subject Error | 23 ( 19.8) | 7 ( 6.4) | 7 ( 9.1) | -- |
| Procedure | 12 ( 10.3) | 0 | 0 | -- |
| Adverse Event | 60 ( 51.7) | 54 ( 49.5) | 54 ( 70.1) | -- |
| Other | 21 ( 18.1) | 15 ( 13.8) | 15 ( 19.5) | -- |
| Number of Patients with Dose Delay | -- | 2 ( 1.8) | -- | 2 ( 6.3) |
| Primary Reason for Dose Delay | | | | |
| Adverse Event | -- | 2 ( 1.8) | -- | 2 ( 6.3) |
| Dose Administration Error | -- | 0 | -- | 0 |
| Equipment Failure | -- | 0 | -- | 0 |
| Other | -- | 1 ( 0.9) | -- | 1 ( 3.1) |
| Number of Patients with Infusion Interruption | -- | 30 ( 27.5) | 14 ( 18.2) | 16 ( 50.0) |
| Primary Reason for Infusion Interruption | | | | |
| Adverse Event | -- | 23 ( 21.1) | 9 ( 11.7) | 14 ( 43.8) |
| Dose Administration Error | -- | 0 | 0 | 0 |
| Equipment Failure | -- | 0 | 0 | 0 |
| First Dose Split | -- | 6 ( 5.5) | 4 ( 5.2) | 2 ( 6.3) |
| Other | -- | 5 ( 4.6) | 3 ( 3.9) | 2 ( 6.3) |

## Numbers analysed

**Table 13.** Analysis populations in Study 20020

| Population | Description | Number of Patients | | |
|---|---|---|---|---|
| | | Arm A | Arm B | Total |
| **ITT** | All randomized patients.<br>Unless otherwise specified, all analyses using the ITT population include only data collected prior to crossover for Arm B patients who crossed over to Arm A, except for OS-related analyses. | 119 | 119<br>82 IdelaR,<br>37 BendaR | 238 |
| **Safety** | All randomized patients who took at least 1 dose (including a partial dose) of study treatment.<br>Unless otherwise specified, all analyses using the Safety population include data collected prior to crossover for Arm B patients who crossed over to Arm A. | 116 | 109<br>77 IdelaR,<br>32 BendaR | 225 |
| **Crossover** | A subpopulation of patients included in the ITT population who were randomized to Arm B and crossed over to receive at least 1 dose of pirtobrutinib. | N/A | 29 | 29 |

## Outcomes and estimation

### Primary endpoint: PFS

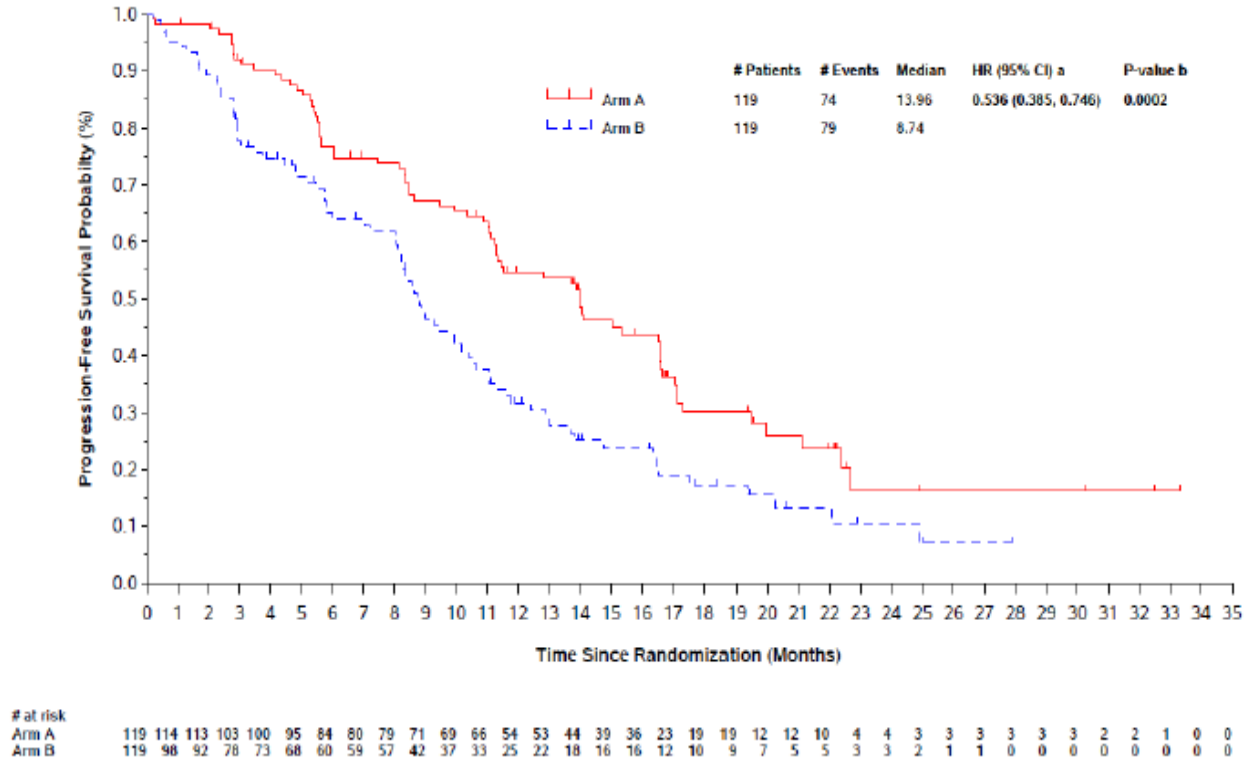
PFS in the primary efficacy analysis is defined as the time from randomisation until the earlier occurrence of documented PD by IRC or death without documented PD.

**Table 14.** Summary of Progression-Free Survival based on IRC Assessments – ITT Population, Study 20020 (DCO: 29 August 2024)

| | **Arm A (n=119)** | **Arm B (n=119)** |
|---|---|---|
| **Number of Events, n (%)** | 74 (62.2) | 79 (66.4) |
| ***PFS (months)*** | | |
| Median (95% CI) | 13.96 (11.24, 16.56) | 8.74 (8.08, 10.38) |
| HR (95%CI) | 0.536 (0.385, 0.746) | |
| p-value | p=0.0002[a] | |
| ***PFS follow-up time (months)*** | | |
| Median (95% CI) | 19.35 (16.66, 22.14) | 17.74 (13.93, 22.90) |

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; PFS = progression-free survival.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

**Figure 9.** Kaplan-Meier plot of PFS based on IRC assessments – ITT Population, Study 20020 (DCO: 29 August 2024)




Abbreviations: Arm A = pirtobrutinib; Arm B = IdelaR or BendaR; CI = confidence interval; HR = hazard ratio; IWRS = interactive web-response system.
[a] Based on the stratified Cox proportional hazards model, with stratification factor from IWRS data: del 17p presence and receipt of prior venetoclax treatment.
[b] 2-sided p-value is based on the stratified log-rank test for comparing Arm A vs. Arm B.

### Key secondary endpoint: OS

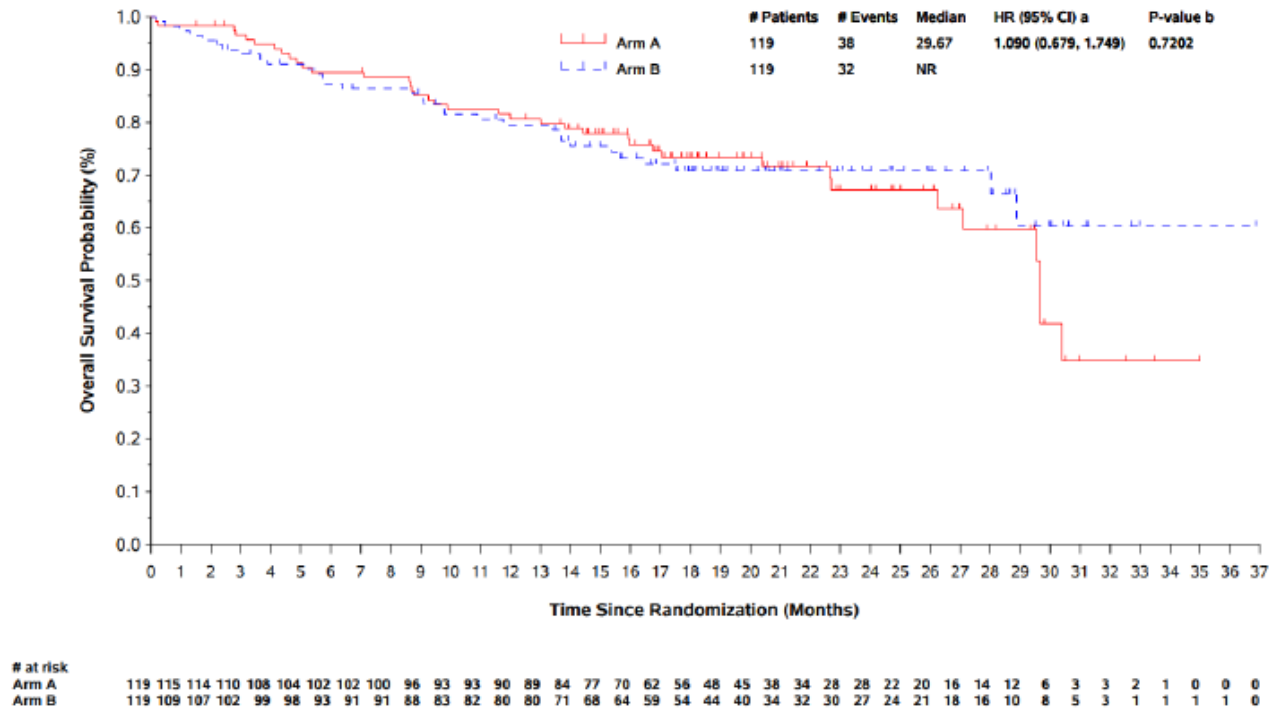
The OS time was measured from the date of randomization to the date of death due to any cause. The final analysis of OS will occur approximately 12 months after the primary analysis of PFS to allow adequate follow-up time for OS assessment.

**Table 15.** Summary of Overall Survival based on Investigator Assessments – ITT Population, Study 20020 (DCO: 29 August 2024)

| | **Arm A (n=119)** | **Arm B (n=119)** |
|---|---|---|
| **Number of Deaths, n (%)** | 38 (31.9) | 32 (26.9) |
| ***OS (months)*** | | |
| Median (95% CI) | 29.67 (27.10, NE) | NR (28.88, NE) |
| HR (95%CI) | 1.090 (0.679, 1.749) | |
| p-value | p=0.7202[a] | |
| ***OS follow-up time (months)*** | | |
| Median (95% CI) | 20.37 (18.23, 21.88) | 19.22 (18.10, 21.60) |

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; NE = not evaluable; NR = not recorded; OS = overall survival.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

**Figure 10.** Kaplan-Meier plot of overall survival - ITT population, Study 20020, including crossover period (DCO: 29 August 2024)




Abbreviations: Arm A = pirtobrutinib; Arm B = IdelaR or BendaR; CI = confidence interval; HR = hazard ratio; IWRS = interactive web-response system.
[a] Based on the stratified Cox proportional hazards model, with stratification factor from IWRS data: del 17p presence and receipt of prior venetoclax treatment.
[b] 2-sided p-value is based on the stratified log-rank test for comparing Arm A vs. Arm B.

### Other secondary endpoints

PFS based on Investigator Assessment

PFS in the secondary efficacy analysis is defined as the time from randomisation until the earlier occurrence of documented PD by Investigator or death without documented PD.

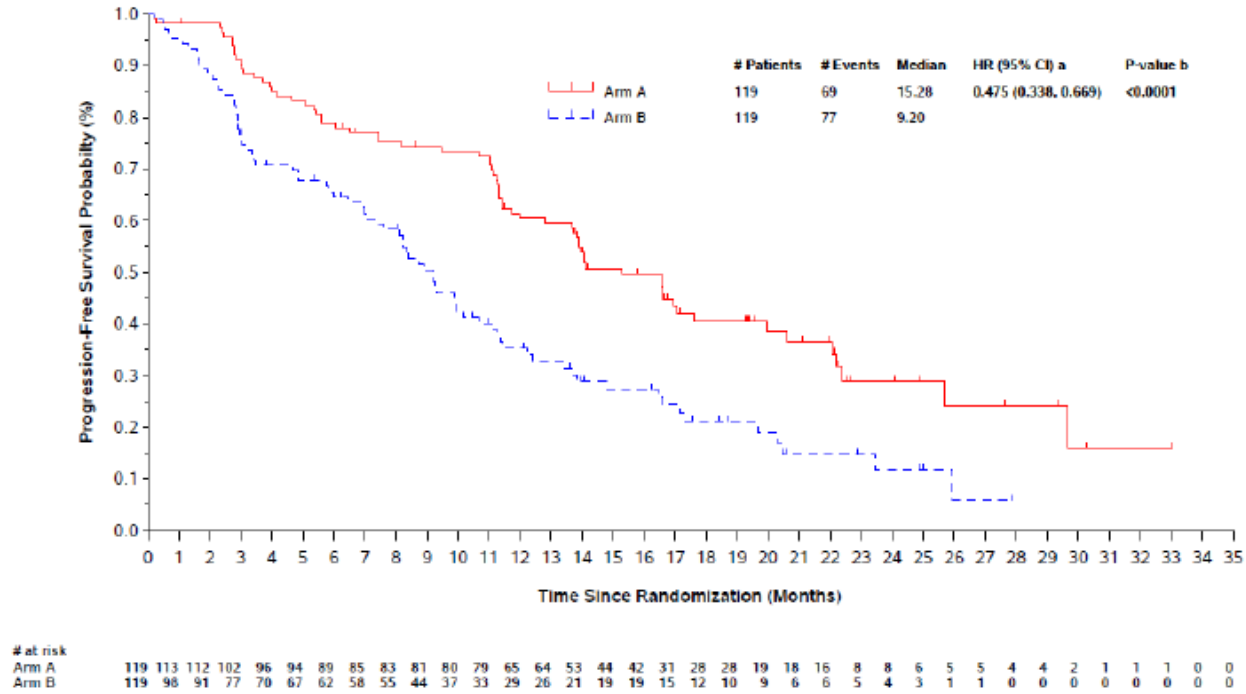
**Table 16.** Summary of Progression-Free Survival based on Investigator Assessments – ITT Population, Study 20020 (DCO: 29 August 2024)

| | **Arm A (n=119)** | **Arm B (n=119)** |
|---|---|---|
| **Number of Events, n (%)** | 69 (58.0) | 77 (64.7) |
| ***PFS (months)*** | | |
| Median (95% CI) | 15.28 (12.81, 19.94) | 9.20 (7.33, 10.64) |
| HR (95%CI) | 0.475 (0.338, 0.669) | |
| p-value | p <0.0001[a] | |
| ***PFS follow-up time (months)*** | | |
| Median (95% CI) | 19.38 (16.72, 21.98) | 17.54 (13.93, 22.90) |

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; PFS = progression-free survival.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; PFS = progression-free survival.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

**Figure 11**. Kaplan-Meier plot of PFS based on investigator assessments – ITT Population, Study 20020 (DCO: 29 August 2024)




Abbreviations: Arm A = pirtobrutinib; Arm B = IdelaR or BendaR; CI = confidence interval; HR = hazard ratio; IWRS = interactive web-response system.
[a] Based on the stratified Cox proportional hazards model, with stratification factor from IWRS data: del 17p presence and receipt of prior venetoclax treatment.
[b] 2-sided p-value is based on the stratified log-rank test for comparing Arm A vs. Arm B.

<u>BOR and ORR based on Investigator and IRC Assessments</u>

ORR is defined as the number of patients who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy divided by the total number of patients randomised to each treatment arm.

**Table 17.** Follow-up analysis of ORR by Investigator Assessment (ITT population, Study 20020 DCO: 29 August 2024)

| | **Arm A (N=119)** | **Arm B (N=119)** |
|---|---|---|
| **ORR, n, (%)** | | |
| ORR, PR or better | 79 (66.4%) | 58 (48.7%) |
| 95% CI | 57.15, 74.78 | 39.47, 58.07 |
| Stratified p-value | P=0.0062[a] | |

Abbreviations: CI = confidence interval; IRC = internal review committee; ITT = intent-to-treat; n = number of patients; ORR = overall response rate; PR = partial response.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value 2-sided based on CMH test stratified by the randomization strata.

**Table 18.** Follow-up analysis of ORR by IRC assessment (ITT population, Study 20020 DCO: 29 August 2024)

| | Arm A (N=119) | Arm B (N=119) |
|---|---|---|
| ***ORR by IRC assessment, n, (%)*** | | |
| ORR, PR or better | 58 (48.7%) | 46 (38.7%) |
| 95% CI | 39.47, 58.07 | 29.87, 48.02 |
| Stratified p-value | p=0.1100[a] | |
| ***ORR by IRC assessment – sensitivity analysis (without confirmation of partial response), n, (%)*** | | |
| ORR, PR or better | 72 (60.5%) | 62 (52.1%) |
| 95% CI | 51.13, 69.34 | 42.75, 61.34 |

Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel; IRC = internal review committee; ITT = intent-to-treat; n = number of patients; ORR = overall response rate; PR = partial response.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value 2-sided based on CMH test stratified by the randomization strata.

DOR based on Investigator and IRC Assessments

DOR is analysed for patients who achieve a BOR of CR, CRi, nPR, or PR. Duration was measured from the date of first response to the date of progression or death due to any cause.

**Table 19.** Summary of DOR by Investigator and IRC assessments (ITT population, Study 20020, DCO: 29 August 2024)

| | Arm A (N=119) | Arm B (N=119) |
|---|---|---|
| ***DOR by Investigator assessment*** | | |
| Median DOR (95%) | 13.86 (11.07, 19.12) | 9.36 (7.23, 13.73) |
| HR (95% CI) | 0.542 (0.337, 0.871) | |
| Stratified p-value | p=0.0104[a] | |
| Median follow-up | 16.46 (13.57, 17.08) | 15.18 (13.37, 20.11) |
| ***DOR by IRC assessment*** | | |
| Median DOR (95%) | 13.77 (11.07, NE) | 11.86 (8.25, 14.75) |
| HR (95% CI) | 0.641 (0.365, 1.126) | |
| Stratified p-value | P=0.1195[a] | |
| Median follow-up | 13.86 (11.07, 16.76) | 17.74 (13.44, 20.11) |

Abbreviations: DOR = duration of response; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

EFS based on Investigator Assessments

EFS is defined as the time from date of randomisation to the date of PD by Investigator or start of new treatment for CLL/SLL or discontinuation from study treatment due to toxicity or death due to any cause, whichever occurs first.

**Table 20**. Summary of EFS based on Investigator Assessments – ITT Population, Study 20020 (DCO: 29 August 2024)

| | **Arm A (n=119)** | **Arm B (n=119)** |
|---|---|---|
| **Number of Events, n (%)** | 77 (64.7) | 94 (76.0) |
| ***EFS (months)*** | | |
| Median (95% CI) | 14.06 (11.40, 16.95) | 7.62 (4.80, 8.80) |
| HR (95%CI) | 0.387 (0.280, 0.534) | |
| p-value | p <0.0001[a] | |
| ***EFS follow-up time (months)*** | | |
| Median (95% CI) | 19.38 (17.15, 22.14) | 18.66 (18.66, NE) |

Abbreviations: CI = confidence interval; EFS= event-free survival; HR = hazard ratio; ITT = intent-to-treat; n = number of patients.
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

Time to next treatment

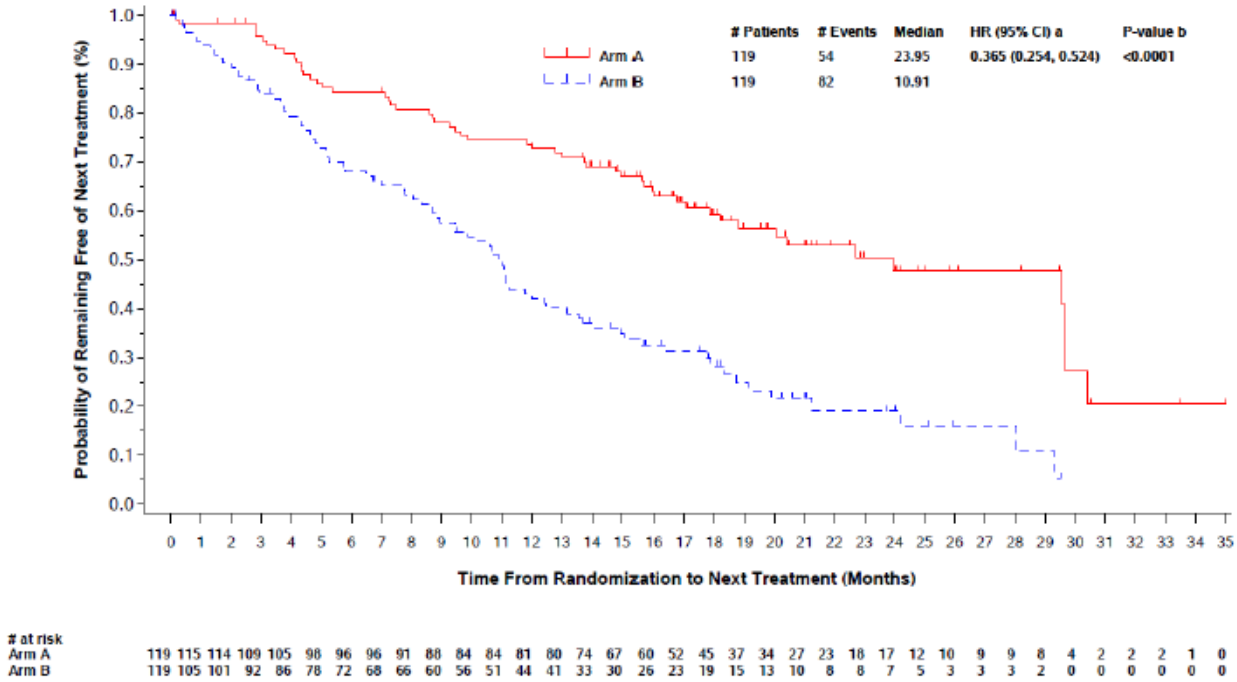
TTNT is defined as time from the date of randomisation to the date of initiation of the subsequent anticancer therapy for CLL/SLL, therapy of pirtobrutinib for Arm B patients who crossover, or death due to any cause, whichever occurs first.

**Table 21**. TTNT based on Investigator Assessments – ITT Population, Study 20020 (DCO: 29 August 2024)

| | **Arm A (n=119)** | **Arm B (n=119)** |
|---|---|---|
| **Number of Events, n (%)** | 54 (45.4) | 82 (68.9) |
| ***TTNT (months)*** | | |
| Median (95% CI) | 23.95 (17.84, 29.67) | 10.91 (8.74, 12.48) |
| HR (95%CI) | 0.365 (0.254, 0.524) | |
| p-value | p <0.0001[a] | |
| ***EFS follow-up time (months)*** | | |
| Median (95% CI) | 20.04 (18.07, 21.42) | 20.24 (16.23, 23.75) |

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; NE = not evaluable; NR= not recorded; TTNT= time to next treatment
[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

**Figure 12**. Kaplan Meier plot of TTNT – ITT population, Study 20020 (DCO: 29 August 2024)




**Patient reported outcomes**

Secondary endpoints of the trial included time to worsening (TTW; also referred to as "Time to Sustained Worsening [TTSW]" in previous documents) of patient-reported CLL/SLL-related symptoms and TTW of physical functioning (PF). Data for those receiving BendaR on Arm B were only evaluated through Week 21, plus the safety follow-up visit on or prior to Week 25. Availability of PRO data through Week 25 only for patients receiving BendaR in Arm B limited the potential to observe PRO worsening events in this study. PRO endpoints in this study were not controlled for type 1 error and thus descriptive in nature.

The TTW of patient-reported CLL/SLL-related symptoms did not show a meaningful difference between treatment arms (HR = 0.97 (95% CI: 0.46, 2.0) in the final PRO analysis.

A favourable trend was shown in TTW of PF, implying potential improvement with pirtobrutinib treatment compared to Arm B, although the 95% CI was fairly large (HR = 0.59 (95% CI: 0.26, 1.33)).

In part due to the relatively short duration of follow-up in which PRO data were collected across both arms (25 weeks), 84.5% of participants in Arm A and 87.8% of participants in Arm B were censored as they did not experience worsening of symptoms at the final PRO analysis as defined in the analysis plan.

Exploratory prespecified endpoints evaluating PROs included longitudinal analyses using mixed models for repeated measures adjusting for baseline scores for CLL/SLL-related symptoms and PF. Within arms, pirtobrutinib demonstrated meaningful (based on published thresholds; Cocks et al. 2012) improvements from baseline in physical function and CLL-related symptoms at all post-baseline assessments in the final PRO analysis (least squares mean change ranged from +5.4 to +8.9 and -7.0 to -11.8, respectively). The control arm demonstrated meaningful improvements at some, still, not all assessments (least squares means change ranged from +0.8 to +4.2 and -0.3 to -5.0, respectively).

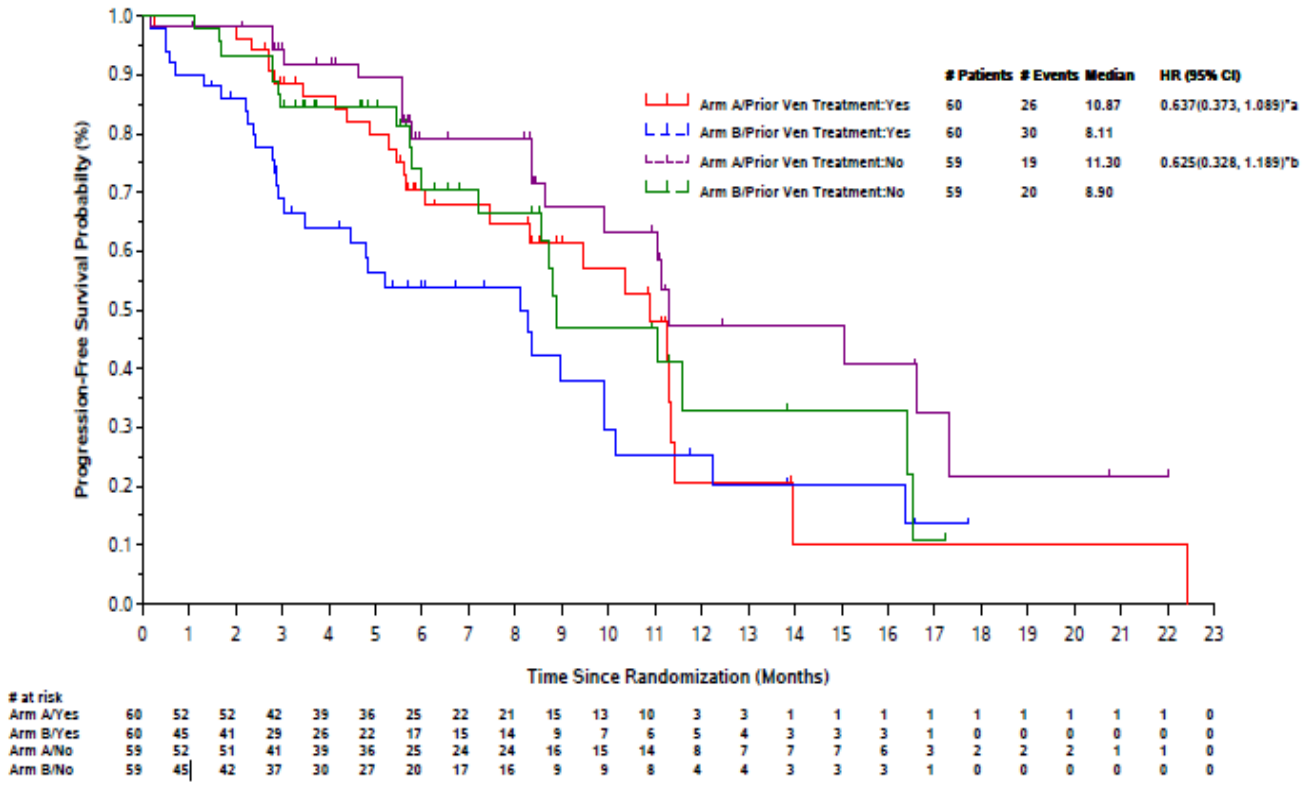
Longer-term data for pirtobrutinib past Week 25 was also evaluated. Median TTW of CLL/SLL-related symptoms was not reached for Arm A until 22.6 months (95% CI: 17.5 – not reached). While comparative analyses include inherent bias due to the lack of randomization (only those who received IdelaR continued to record PRO endpoints on the control arm), it should be noted that median TTW of CLL/SLL-related symptoms in these longer-term analyses for IdelaR was 16.4 months (95% CI: 13.6 – not reached) Median TTW of PF was 20.3 months (95% CI: 14.5, not reached) for pirtobrutinib in the longer-term analysis. Again, caution should be taken to avoid making comparisons, given that data were only collected for the IdelaR portion of the control arm (longer-term TTW of PF for IdelaR is 17.5 months, 95% CI: 13.6, not reached)

## Ancillary analyses

IRC-assessed PFS

An unstratified analysis of IRC-assessed PFS was performed to evaluate the potential differences observed based on the IWRS randomization stratification factors of deletion 17p presence and prior venetoclax treatment.

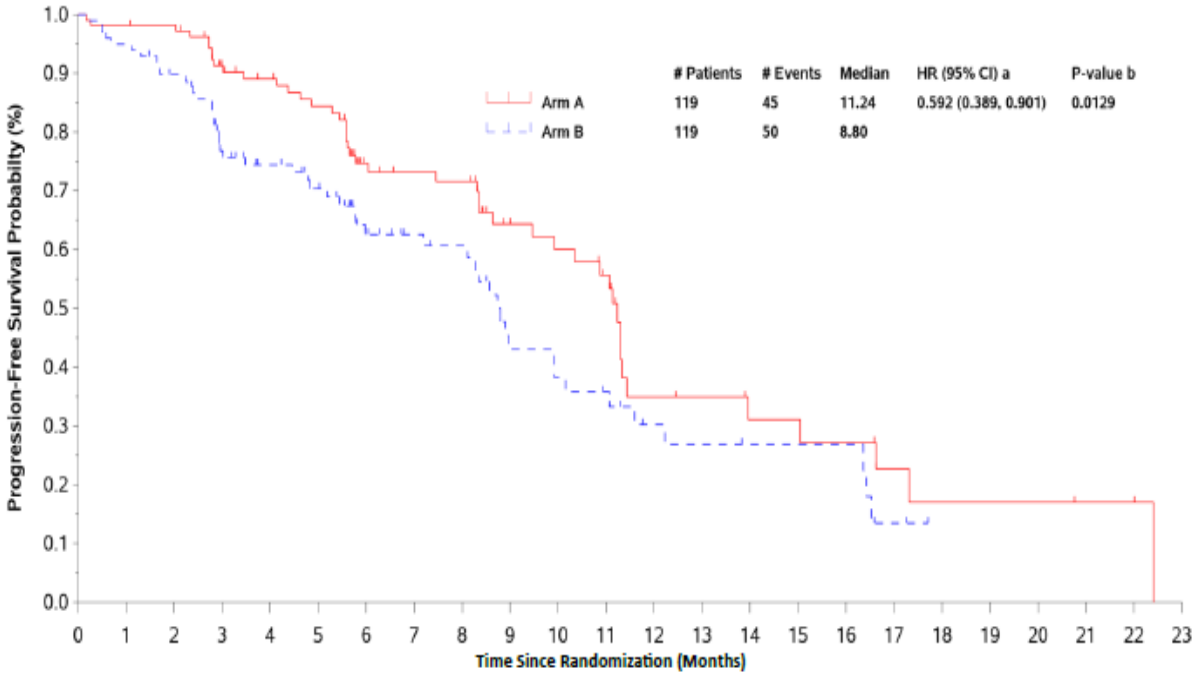
**Figure 13.** Kaplan-Meier Plot of Progression-free Survival Based on IRC Assessments by Prior Venetoclax Treatment - ITT Population, Study 20020, (DCO: 29 August 2023)



**Sensitivity analyses**

**Figure 14** presents an analysis of PFS by including events after subsequent anticancer therapy (i.e., without censoring patients who received subsequent anticancer therapy to the last adequate assessment prior to the subsequent anticancer therapy), with an HR = 0.592 (95% CI: 0.389, 0.901; p = 0.0129).

**Figure 14.** Kaplan-Meier Plot of Progression-Free Survival Based on IRC Assessments – Sensitivity Analysis – without Censoring for New Anti-Cancer Therapy, (DCO: 29 August 2023)




[a] Based on the stratified Cox proportional hazards model, with stratification factor from IWRS data: del 17p presence and receipt of prior venetoclax treatmen

[b] 2-sided p-value is based on the stratified log-rank test for comparing Arm A versus Arm B.

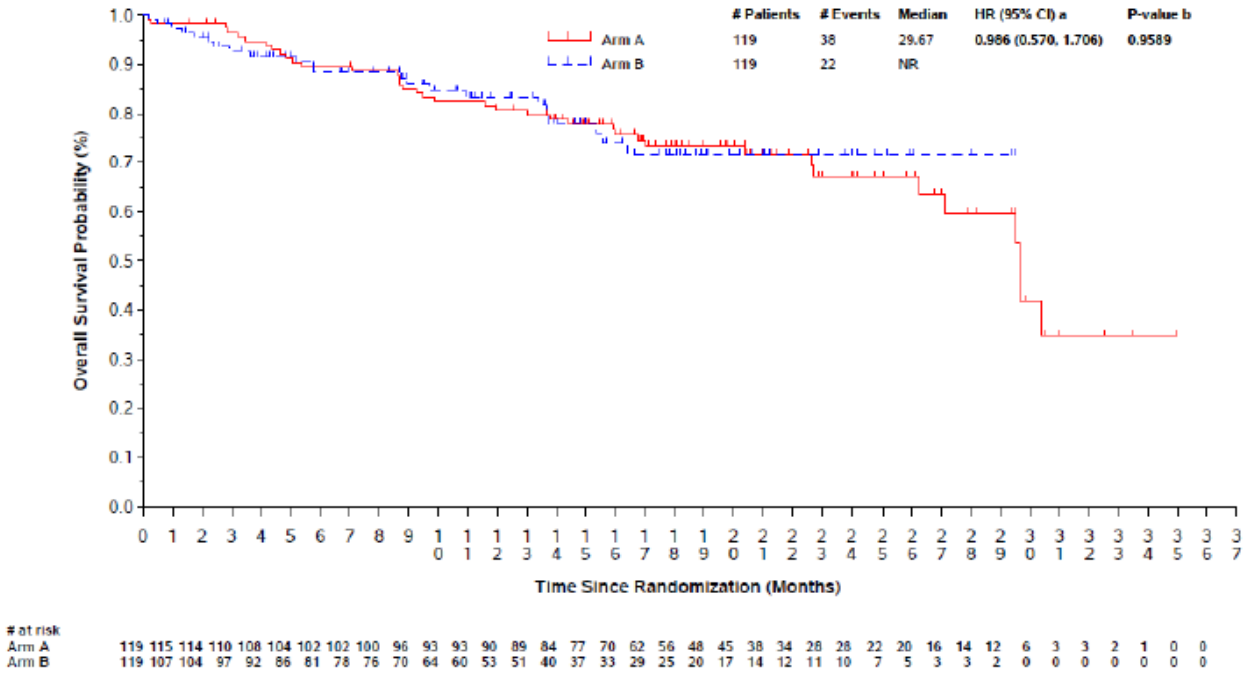
Analysis including IRC-assessed PFS events (PD or death) after 2 or more consecutively missed showed an HR = 0.575 (95% CI: 0.380, 0.870; p = 0.0078) (*DCO: 29 August 2023*).

Analysis of PFS events excluding patients with important protocol deviations showed an HR = 0.576 (95% CI: 0.377, 0.879; p = 0.0093), respectively (*DCO: 29 August 2023*).

Overall survival

A prespecified sensitivity analysis of OS was performed as described in the SAP v3.0 and was conducted for censoring of patients who crossed over from Arm B to Arm A at the time of crossover by August 2024 data cut.

**Figure 15.** Kaplan-Meier plot of overall survival – sensitivity analysis-censor patients at crossover (ITT population, Study 20020), data cut-off 29 Aug 2024.




By censoring those patients at crossover, the naïve method relies on a crude adjustment that discards information collected after crossover. After censoring the 50 patients who crossed over from Arm B to pirtobrutinib, the naïve method yielded an adjusted OS HR of 0.986 (95% CI: 0.570, 1.706; p=0.9589).

- Inverse Probability of Censoring Weighting (IPCW)

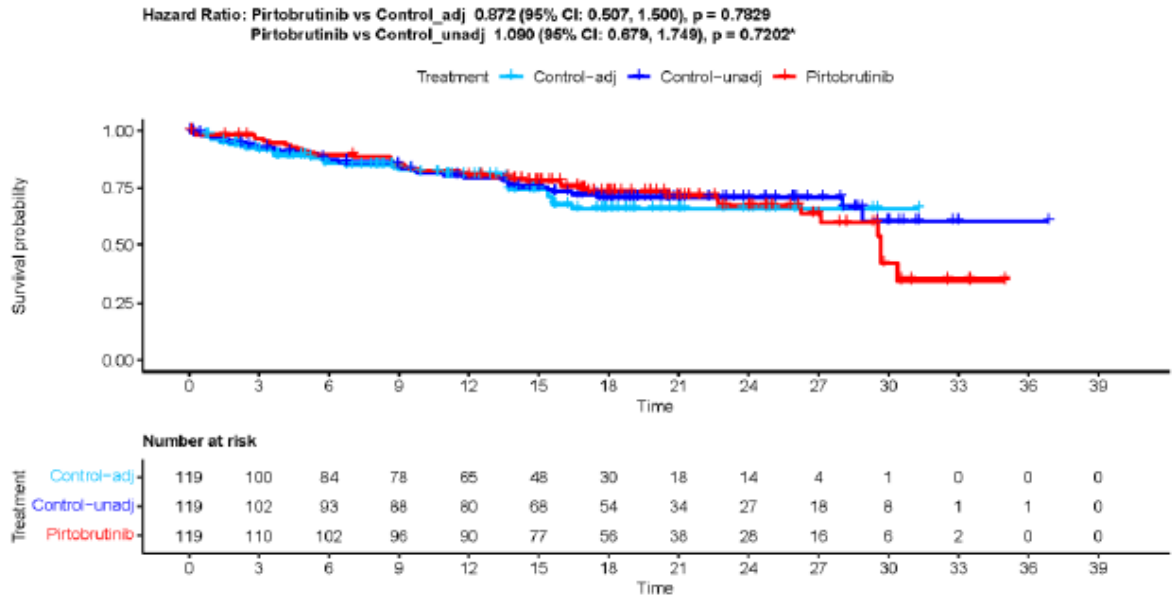
The IPCW method accounts for crossover effect by censoring crossover patients at the time of PD and reweighting remaining patients in the control arm who had PD but did not crossover (Latimer 2012; Latimer 2013). The reweighting considers the predicted probability of crossover based on the most relevant baseline prognostic factors as well as the predicted probability of crossover among patients with PD based on the most relevant prognostic factors measured at PD (i.e., second baseline covariates); if prognostic factors at PD are unavailable, baseline covariates may be used.

A number of known CLL/SLL prognostic factors were considered as covariates in the model. Using random forest-based model selection approach, the following baseline covariates for all patients in the control arm or second baseline covariates for PD patients were included:

- Baseline covariates: number of prior lines of therapy (≤3 versus >3 lines), reason for discontinuation from most recent BTKi (due to PD versus not due to PD), beta-2 microglobulin (≤3.5 versus >3.5 mg/L)
- Second baseline covariates for patients with PD: reason for discontinuation from most recent BTKi (due to PD versus not due to PD), ECOG performance status (0-1 versus 2) at PD, bulky disease (<5 versus ≥5 cm) at baseline

In addition, OS time is adjusted for in both the baseline covariate and second baseline covariate models.

**Figure 16.** Kaplan-Meier plot of overall survival including predicted survival for the control arm after adjusting for crossover by the IPCW method, Study 20020 (DCO: 29 August 2024)




Abbreviations: IPCW = Inverse Probability of Censoring Weighting method; CI = Confidence Interval; adj = Adjusting for Treatment Switching; unadj = Unajusting for Treatment Switching.
* 2−sided p−value is based on the unstratified log−rank test for comparing Pirtobrutinib vs Control. Stratified for unadjustment

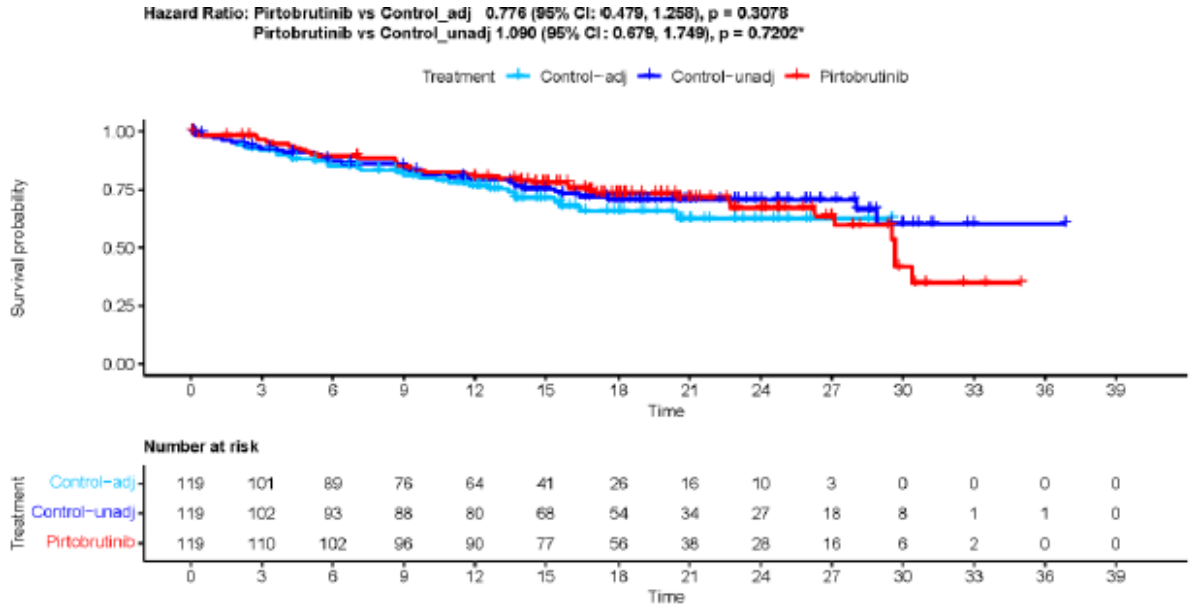
Implementing the IPCW method-based weights in a weighted Cox regression model resulted in an adjusted OS HR of 0.872 (95% CI: 0.507, 1.500), suggesting crossover impact on OS.

- Two-stage Accelerated Failure Time (Two-stage AFT)

To mitigate the treatment effect with pirtobrutinib after crossover, the Two-stage AFT model estimates counter-factual survival for the control arm as if crossover had never occurred (Latimer et al. 2020). This approach applies a "shrinking factor" to the survival time after crossover, which adjusts the OS outcomes in the control arm by scaling down survival times for crossover patients. The shrinking factor is estimated by comparing post-progression survival between crossover and non-crossover patients within the control arm, while accounting for strongly associated second baseline covariates.

The second baseline covariates included in the models are: reason for discontinuation from most recent BTKi (due to PD versus not due to PD), ECOG performance status (0-1 vs. 2) at PD, bulky disease (< 5 vs. ≥5 cm) at baseline, as well as progression-free survival time. These covariates ensure that the shrinking factor captures the influence of clinical characteristics that are likely to affect survival after crossover.

**Figure 17.** Kaplan-Meier plot - Two-stage AFT model adjusted OS (DCO: 29 August 2024)




Abbreviations: CI = Confidence Interval; adj = Adjusting for Treatment Switching; unadj = Unajusting for Treatment Switching; AFT = Accelerated Failure Time.
* 2-sided p-value is based on the unstratified log-rank test for comparing Pirtobrutinib vs Control. Stratified for unadjustment

After applying the shrinking factor, the Two-stage AFT model adjusted OS HR of 0.776 (95% CI: 0.479, 1.258) signified a potentially meaningful impact of crossover on OS.

**Subgroups analyses**

PFS based on IRC assessments

Subgroup analyses of PFS based on IRC assessments are presented in **Figure 18**-**20**.

**Figure 18.** Forest Plot of PFS Based on IRC Assessments by Demographics – ITT Population, Study 20020 (DCO: 29 August 2024)

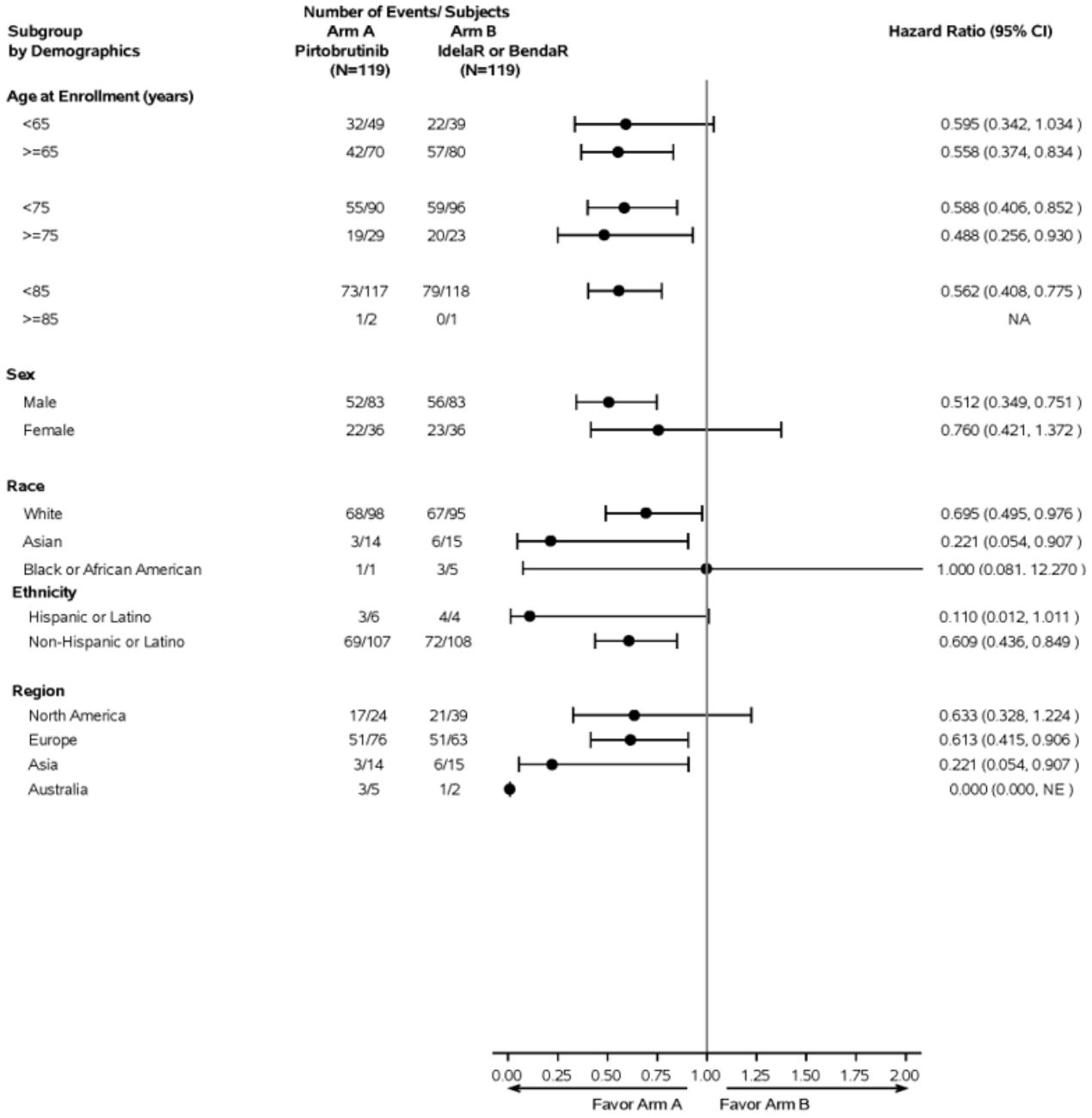



**Figure 19**. Forest Plot of PFS Based on IRC Assessments by Prior Therapy – ITT Population, Study 20020 (DCO: 29 August 2024)

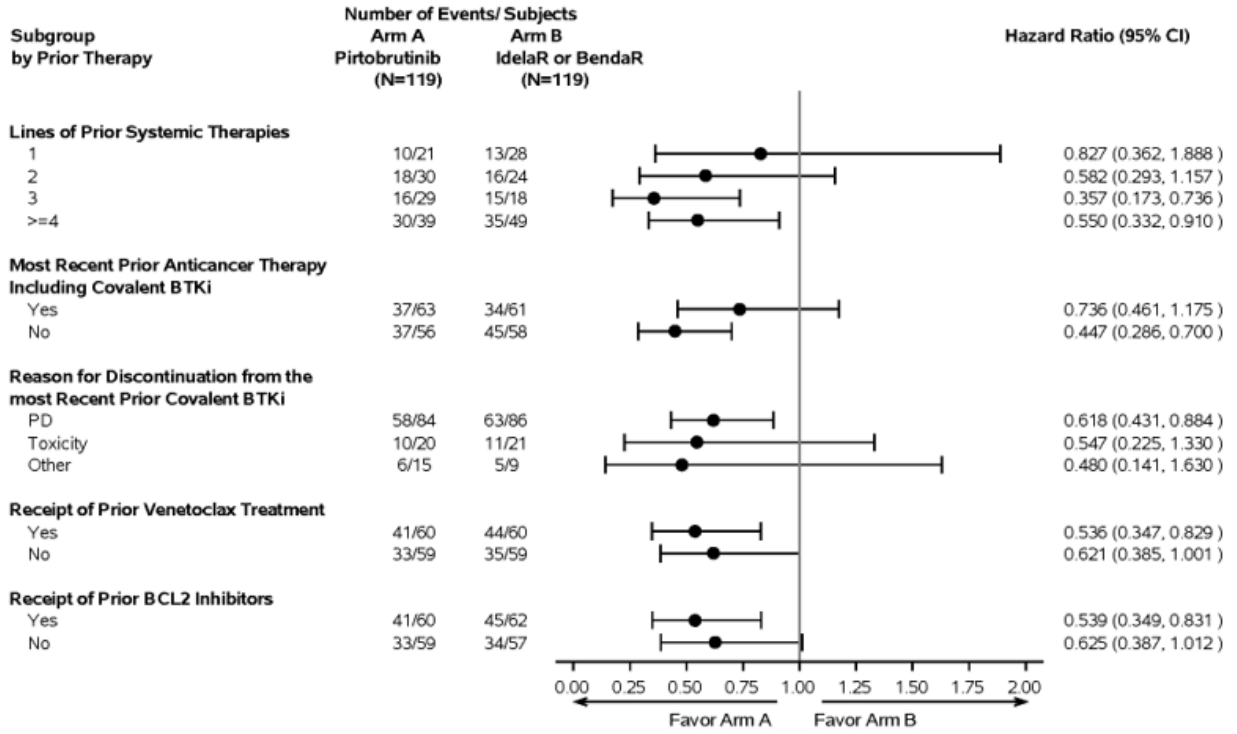
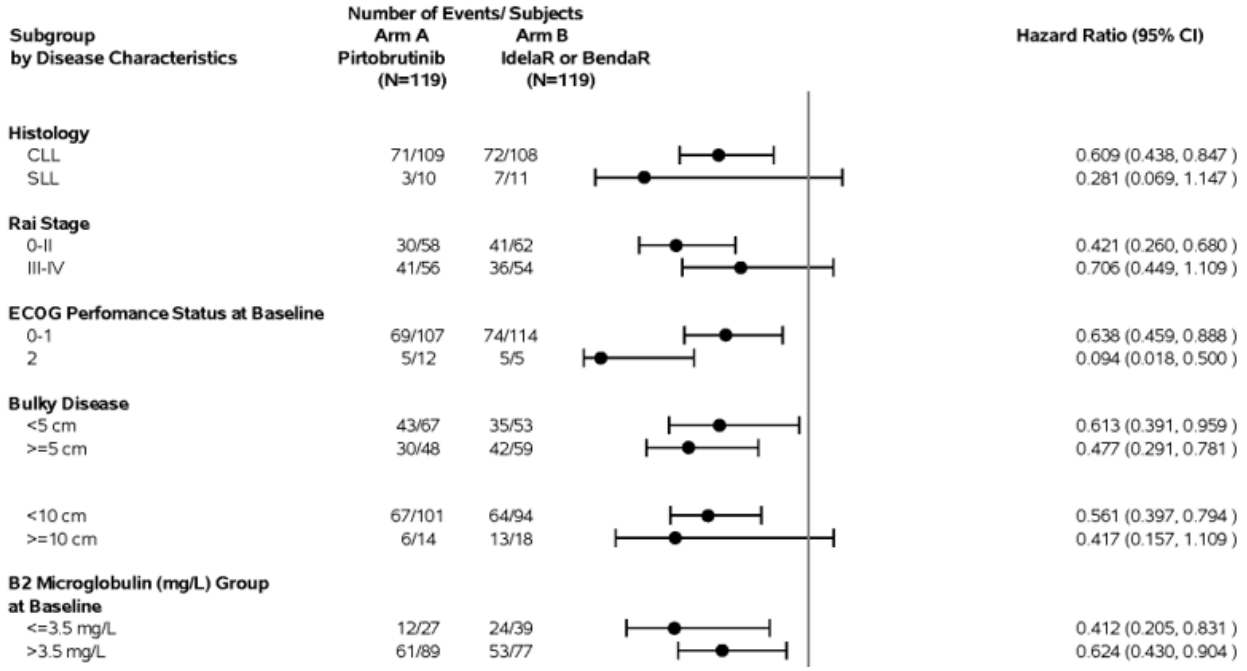
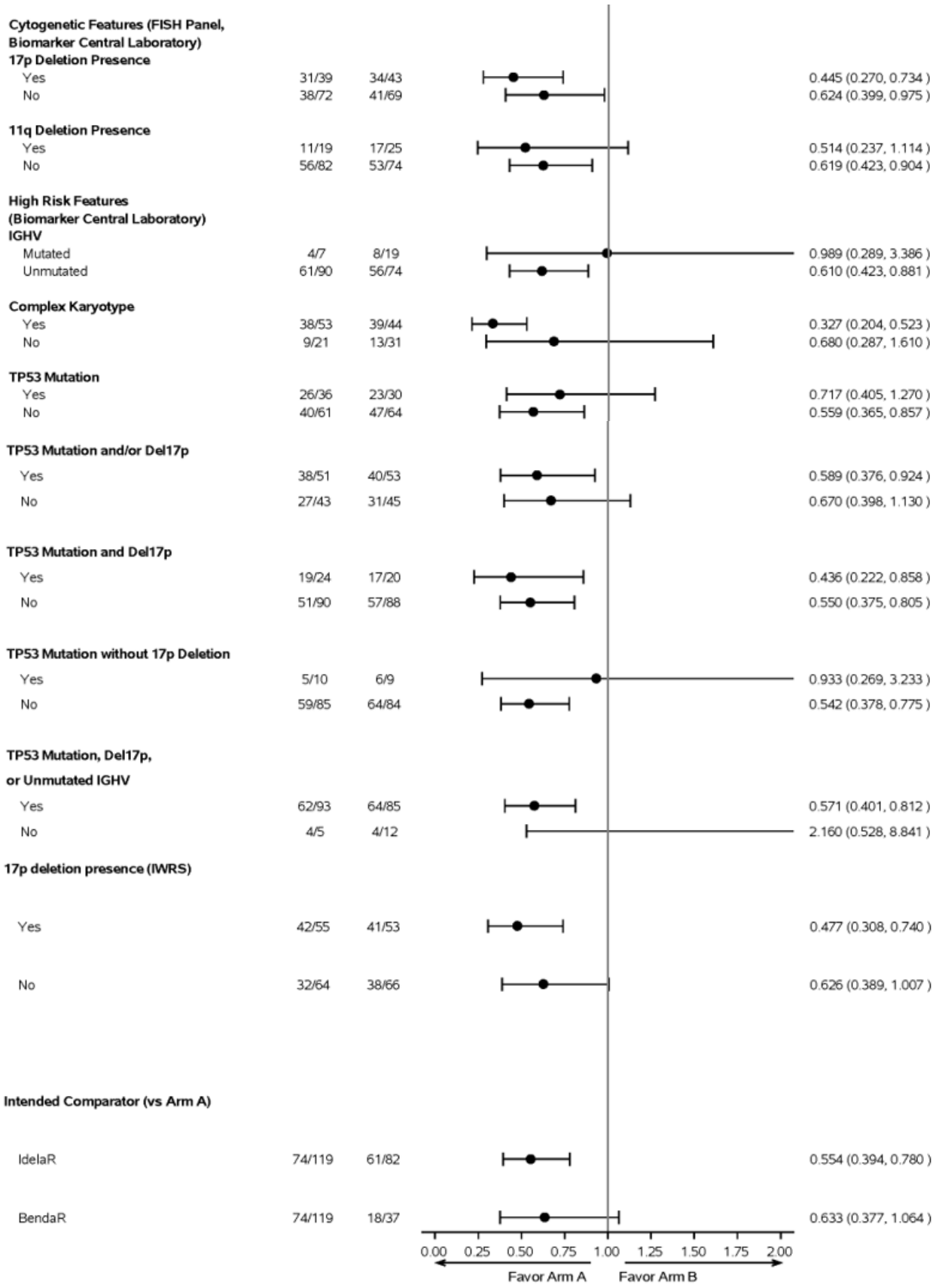



**Figure 20**. Forest Plot of PFS Based on IRC Assessments by Disease Characteristics – ITT Population, Study 20020 (DCO: 29 August 2024)




Cytogenetic Features (FISH Panel, Biomarker Central Laboratory)
17p Deletion Presence
Yes 31/39 34/43 0.445 (0.270, 0.734 )
No 38/72 41/69 0.624 (0.399, 0.975 )
11q Deletion Presence
Yes 11/19 17/25 0.514 (0.237, 1.114 )
No 56/82 53/74 0.619 (0.423, 0.904 )
High Risk Features (Biomarker Central Laboratory)
IGHV
Mutated 4/7 8/19 0.989 (0.289, 3.386 )
Unmutated 61/90 56/74 0.610 (0.423, 0.881 )
Complex Karyotype
Yes 38/53 39/44 0.327 (0.204, 0.523 )
No 9/21 13/31 0.680 (0.287, 1.610 )
TP53 Mutation
Yes 26/36 23/30 0.717 (0.405, 1.270 )
No 40/61 47/64 0.559 (0.365, 0.857 )
TP53 Mutation and/or Del17p
Yes 38/51 40/53 0.589 (0.376, 0.924 )
No 27/43 31/45 0.670 (0.398, 1.130 )
TP53 Mutation and Del17p
Yes 19/24 17/20 0.436 (0.222, 0.858 )
No 51/90 57/88 0.550 (0.375, 0.805 )
TP53 Mutation without 17p Deletion
Yes 5/10 6/9 0.933 (0.269, 3.233 )
No 59/85 64/84 0.542 (0.378, 0.775 )
TP53 Mutation, Del17p, or Unmutated IGHV
Yes 62/93 64/85 0.571 (0.401, 0.812 )
No 4/5 4/12 2.160 (0.528, 8.841 )
17p deletion presence (IWRS)
Yes 42/55 41/53 0.477 (0.308, 0.740 )
No 32/64 38/66 0.626 (0.389, 1.007 )
Intended Comparator (vs Arm A)
IdelaR 74/119 61/82 0.554 (0.394, 0.780 )
BendaR 74/119 18/37 0.633 (0.377, 1.064 )
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Favor Arm A
Favor Arm B

* There was insufficient data to provide reliable estimates on the HR and 95% CI for certain subgroups (Asian, Black or African American, Australian). 95% CI was not estimated for subgroups that had 0 events in 1 or both of the treatment arms.

Note: For the column "Most Recent Prior Anticancer Therapy including Covalent BTKi": Yes = most recent therapy included covalent BTK inhibitor; No = most recent therapy did not include covalent BTK inhibitor.

Efficacy Data in Crossover Patients

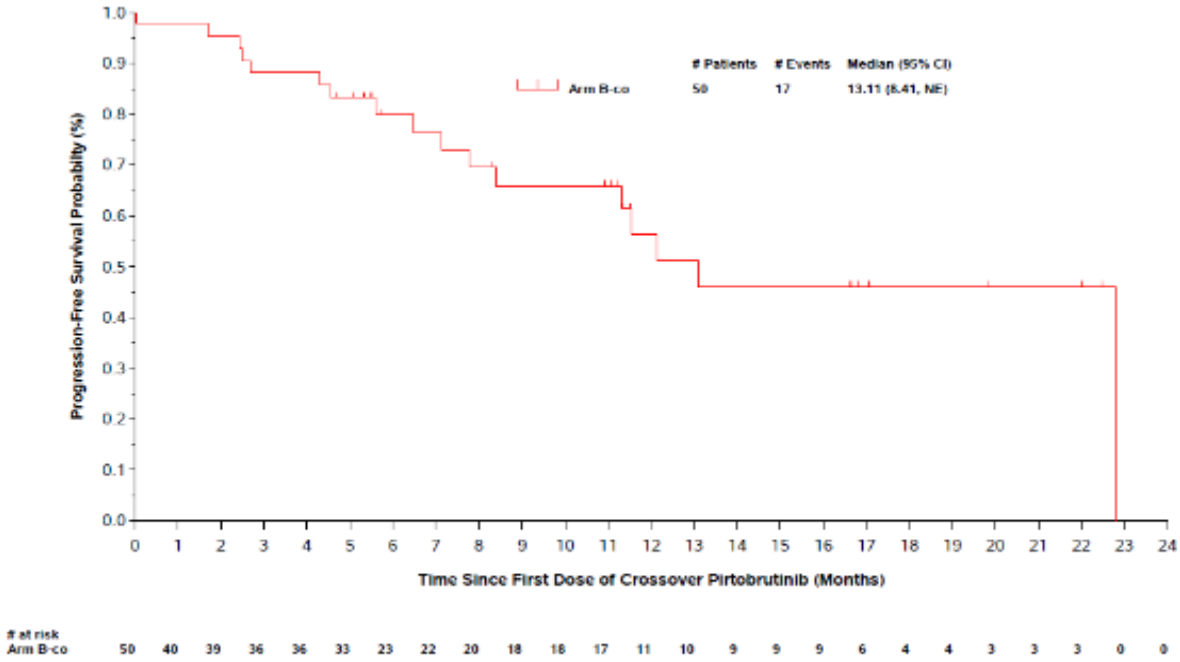
- PFS

**Table 22**. Summary of Progression-Free Survival based on Investigator Assessments (Crossover Population, Study 20020)

| | **Follow-Up Analysis Data Cut: 29 August 2024** |
|---|---|
| | **Arm B (IdelaR or BendaR) Crossover to Pirtobrutinib (n=50)** |
| **Number of Events, n (%)** | 17 (34.0) |
| **PFS (months)** | |
| Median PFS (95% CI) | 13.11 (8.41, NE) |
| **PFS Follow-Up Time (months)** | |
| Median (95% CI) | 11.07 (5.55, 16.69) |

Abbreviations: CI = confidence interval; n = number of patients; PFS = progression-free survival.

**Figure 21**. Kaplan-Meier plot of progression-free survival based on investigator assessments (crossover population), Study 20020, data cut-off 29 Aug 2024




Abbreviations: Arm B = IdelaR or BendaR; CI = confidence interval; NE = not evaluable.

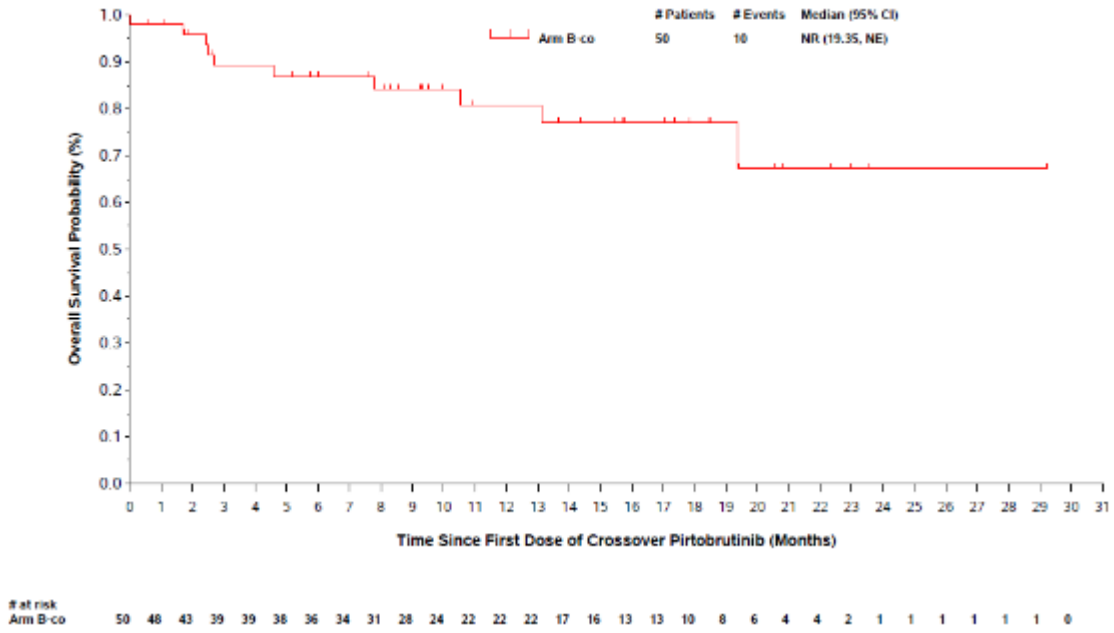
- OS

**Table 23**. Summary of Final Overall Survival (Crossover Population), Study 20020, data cut-off 29 Aug 2024

| | Follow-Up Analysis<br>Data Cut: 29 August 2024 |
|---|---|
| | Arm B (IdelaR or BendaR) Crossover to Pirtobrutinib (n=50) |
| **Number of Deaths, n (%)** | 10 (20.0) |
| **OS (months)** | |
| Median Survival (95% CI) | NR (19.35, NE) |
| **OS Follow-Up Time (months)** | |
| Median (95% CI) | 13.63 (9.26, 15.74) |

Abbreviations: Arm B = IdelaR or BendaR; CI = confidence interval; n = number of patients; NE = not evaluable; NR = not recorded; OS = overall survival.

**Figure 22.** Kaplan-Meier plot of overall survival (crossover population), Study 20020, data cut-off 29 Aug 2024.




## *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 24.** Summary of Efficacy for trial 20020

| **Title: A Phase 3 Open-Label, Randomised Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukaemia / Small Lymphocytic Lymphoma (BRUIN-CLL-321)** | |
|---|---|
| Study identifier | Protocol No.: LOXO-BTK-20020 (also Study 20020, J2N-OX-JZNN)<br>EudraCT No.: 2020-004554-30 |
| Design | Study 20020 is a Phase 3 global, randomised, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to Investigator's choice of either IdelaR or BendaR (Arm B) in CLL / SLL patients who have been treated with a covalent BTK inhibitor, approved (ibrutinib, acalabrutinib, or zanubrutinib) or investigational. Eligible patients were randomized 1:1 to Arm A:Arm B, based on stratification factors of deletion 17p presence (yes / no) and receipt of prior venetoclax treatment (yes / no). |
| Hypothesis | <u>For Patients with CLL / SLL Previously Treated with a BTK Inhibitor</u><br>• Treatment with pirtobrutinib as continuous monotherapy will provide superior PFS (assessed by IRC) over treatment with Investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients with covalent BTK inhibitor pretreated CLL / SLL.<br>• The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in the hierarchical order:<br>- IRC-assessed PFS, then<br>- OS.<br>The final analysis of OS will occur approximately 12 months after the primary analysis of PFS to allow adequate follow-up time for OS assessment or when approximately 70 OS events have been observed. |

| | | | |
|---|---|---|---|
| Treatments groups | Arm A | | 200 mg PO QD every 28 days until disease progression or unacceptable toxicity, 119 patients randomized |
| | Arm B:<br>Investigator's choice of<br>• idelalisib plus rituximab, or<br>• bendamustine plus rituximab. | | • Idelalisib (150 mg PO BID, every 28 days continuously until disease progression or unacceptable toxicity) plus rituximab (375 mg/m² on C1D1 for the first 28 day cycle and then 500 mg/m² every 2 weeks for 4 doses (C1D15, C2D1, C2D15, and C3D1), and then every 4 weeks for 3 doses (C4D1, C5D1, and C6D1) for a total of 8 doses), 82 patients randomized<br>OR<br>• Bendamustine (6 cycles at 70 mg/m² IV on Days 1 and 2 of each cycle) plus rituximab (375 mg/m² Day 1 of the first cycle and 500 mg/m² Day 1 of Cycles 2 to 6), 37 patients randomized |
| Endpoints and definitions | Primary endpoint | PFS as assessed by IRC per iwCLL 2018 criteria | PFS as assessed by IRC is defined as the time from randomization until the occurrence of documented disease progression by the IRC, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD |
| | Key secondary endpoint | OS as assessed by Investigator | OS as assessed by Investigator is defined as the time from randomization until death from any cause |
| | Supportive secondary endpoints | PFS as assessed by Investigator per iwCLL 2018 criteria | PFS as assessed by the Investigator is defined as the time from randomization until the earlier occurrence of documented PD by Investigator, per iwCLL 2018 criteria, or death without documented PD. |
| | | ORR as assessed by the Investigator and IRC | ORR according to IRC-assessed best overall response (BOR) is defined as the number of patients who achieve a BOR of complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR) or PR at or before the initiation of subsequent anticancer therapy divided by the total number of patients randomized to each treatment arm. |
| | | DOR as assessed by Investigator and IRC | DOR as assessed by Investigator and IRC is defined as the time from the date of the first documented response until the first date of the documentation of PD per iwCLL 2018 criteria, or the date of death from any cause in the absence of documented PD. |
| | | EFS as assessed by Investigator | EFS is defined as the time from date of randomisation to the date of PD or start of new treatment for CLL or discontinuation from treatment due to toxicity, or death, whichever occurs first. |
| | | TNTT as assessed by Investigator | TTNT is defined as the time from the date of randomisation to the date of the next systemic anticancer therapy for CLL or death, whichever occurs first |
| Database lock | 29 August 2024 | | |

| **Results and Analysis** | | | |
|---|---|---|---|
| **Analysis description** | **Follow-up analysis** | | |
| Analysis population and time point description | Intent to treat (ITT): all randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment arm they were assigned to regardless of what actual treatment they receive. | | |
| Descriptive statistics and estimate variability | Treatment group | Arm A : Pirtobrutinib | Arm B IdealaR or BendaR |
| | Number of subject | n=119 | n=119 (82 IdelaR, 37 BendaR) |
| | PFS by IRC: median, months (95% CI) | 13.96 (11.24, 16.56) | 8.74 (8.08, 10.38) |
| | OS by INV: median, months (95% CI) | 29.67 (27.10, NE) | NR (28.88, NE) |
| | PFS by INV: median, months (95% CI) | 15.28 (12.81, 19.94) | 9.20 (7.33, 10.64) |
| | ORR by INV: % (95% CI) | 66.4 (57.15, 74.78) | 48.7 (39.47, 58.07) |
| | ORR by IRC: % (95% CI) | 48.7 (39.47, 58.07) | 38.7 (29.87, 48.02) |
| | DOR by INV: median, months (95% CI) | 13.86 (11.07, 19.12) | 9.36 (7.23, 13.73) |
| | DOR by IRC: median, months (95% CI) | 13.77 (11.07, NE) | 11.86 (8.25, 14.75) |
| | EFS by INV: median, months (95% CI) | 14.06 (11.40, 16.95) | 7.62 (4.80, 8.80) |
| | TTNT: median, months (95% CI) | 23.95 (17.84, 29.67) | 10.91 (8.74, 12.48) |
| Effect estimate per comparison | | Comparison groups | Arm A vs Arm B |
| | Primary endpoint: PFS by IRC | Hazard ratio ([HR] 95% CI) | 0.536 (0.385, 0.746) |
| | | P-value | 0.0002[a] |
| | Key secondary endpoint: OS by INV | HR (95% CI) | 1.090 (0.679, 1.749) |
| | | P-value | 0.7202[a] |
| | Supportive secondary endpoint: PFS by INV | HR (95% CI) | 0.475 (0. 338, 0.669) |
| | Supportive secondary endpoint : ORR by IRC | P-value | 0.1100[b] |
| | Supportive secondary endpoint : ORR by INV | P-value | 0.0062[b] |
| | Supportive secondary endpoint: DOR by INV | HR (95% CI) | 0.542 (0.337, 0.871) |

| | | | |
|---|---|---|---|
| | Supportive secondary endpoint: DOR by IRC | HR (95% CI) | 0.641 (0.365, 1.126) |
| | Supportive secondary endpoint: EFS by INV | HR (95% CI) | 0.387 (0.280, 0.534) |
| | Supportive secondary endpoint: TTNT by INV | HR (95% CI) | 0.365 (0.254, 0.524) |
| Notes | Patient-reported outcomes (PRO) of TTSW of CLL/SLL symptoms and physical functioning are not presented above but it should be noted that the corresponding medians were not reached by 29 August 2023. No updates were provided by August 2024 data cut. | | |

Abbreviations: BID = twice daily; BOR = best overall response; BTK = Bruton's tyrosine kinase; CI = confidence interval; CLL = chronic lymphocytic leukaemia; CR = complete response; C = cycle; D = day; DOR = duration of response; EFS = event free survival; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; HR = hazard ratio; ITT = intent to treat; INV = investigator; IRC = independent review committee; IV = intravenous(ly); iwCLL = International Working Group CLL; NE = not estimable; NR = not reached; No. = number; ORR = overall response rate; OS = overall survival; PAS = Primary Analysis Set; PD = progressive disease; PFS = progression-free survival; PO = by mouth; PR = partial response; PRO = patient-reported outcome; QD = once daily; SLL = small lymphocytic lymphoma; TTNT = time to next treatment; TTSW = time to sustained worsening.

[a] This analysis was descriptive and not alpha-controlled for statistical testing. P-value is 2-sided based on stratified log-rank test.

[b] 2-sided p-value based on CMH test stratified by the randomization strata.

## *Supportive study*

Study 18001 is an open-label, multicenter Phase 1/2 study of oral pirtobrutinib to evaluate safety and efficacy in patients with CLL/SLL and B-cell NHL who have failed or were intolerant to standard of care.

This study is ongoing and includes 2 portions:

1) The monotherapy portion includes Phase 1 dose escalation and dose expansion and Phase 2.
2) The combination therapy Phase 1b portion is a safety assessment and expansion of pirtobrutinib plus venetoclax with or without rituximab (or biosimilar anti-CD20 therapy).

- Cohort 2 CLL/SLL: Confirmed diagnosis of CLL/SLL by iwCLL 2018 criteria and treated with 2 or more prior regimens, including a BTK inhibitor-containing regimen
- Cohort 7: Defined as CLL/SLL or NHL not otherwise specified in Cohorts 1 through 6, inclusive of CLL/SLL or NHL, Richter's transformation, or low-grade NHL with transformation, blastoid MCL, and/or patients with history of CNS involvement or primary CNS lymphoma.

The primary objective of the Phase 2 portion of the study is to assess the preliminary antitumor activity of pirtobrutinib based on ORR as assessed by an IRC.

As of the 08 February 2023 data cut-off, 227 (86.3%) patients in Cohort 2 had received at least 1 dose of pirtobrutinib at the RP2D (200 mg QD) and 251 (95.4%) patients had received at least 1 dose of pirtobrutinib at 200 mg QD or higher. In this cohort, 155/263 patients (58.9%) with CLL are still on study, with 91 patients (34.6%) still receiving pirtobrutinib.

The median time on treatment was 18.40 months (range: 0.2 to 46.2). The most common reasons for treatment discontinuation in Cohort 2 were PD (103 [39.2%]), AEs (26 [9.9%]), and death (17 [6.5%]).

Similar to patients in Cohort 2, most patients with CLL/SLL in Cohort 7 (13/19 patients [68.4%]) are still on study, with 9 patients (47.4%) still receiving pirtobrutinib. Per study design, all (100%) patients in Cohort 7 had received at least 1 dose of pirtobrutinib at the RP2D (200 mg QD) as of the 08 February 2023 data cut-off. The median time on treatment was 22.34 months (range: 0.9 to 33.5). The most common reasons for treatment discontinuation in Cohort 7 were PD (7 [36.8%]) and AEs (2 [10.5%]).

A total of 263 patients with CLL/SLL were evaluated in Cohort 2 and 19 patients with CLL/SLL were evaluated in Cohort 7. Most patients with CLL/SLL evaluated in Cohorts 2 and 7 were male (68.1% and 68.4% of patients, respectively) and White (90.9% and 94.7% of patients, respectively).

The median age of patients with CLL/SLL in Cohort 2 and in Cohort 7 was 68.0 and 70.0 years, respectively (range: 36 to 88 years for Cohort 2; 49 to 87 years for Cohort 7). In Cohort 2, 63.9% of patients enrolled were age 65 and older; in Cohort 7, this group totaled 68.4%. The median body weight for Cohorts 2 and 7 was 80.00 kg (range: 37.5 to 152.5 kg) and 80.50 kg (range: 50.5 to 129.4 kg), respectively.

For patients in Cohort 2, the median time from initial diagnosis of CLL/SLL to first dose of pirtobrutinib was 139.48 months (range: 8.2 to 374.5 months). The median time from initial diagnosis of CLL to first dose in Cohort 7 was 93.67 months (range: 10.9 to 342.7 months). The majority of patients with CLL enrolled with an ECOG PS of either 0 (134 [51.0%] patients in Cohort 2 and 10 (52.6) patients in Cohort 7) or 1 (109 [41.4%] patients in Cohort 2 and 9 [47.4%] patients in Cohort 7). A baseline score of Rai Stage of II or higher was reported in 170 (64.6%) patients in Cohort 2 and 14 (73.7%) patients in Cohort 7, respectively. In Cohort 2, 261 (99.2%) patients had disease classified as CLL and 2 (0.8%) patients as SLL. In Cohort 7, all 19 patients had disease classified as CLL.

**Outcomes**

Cohort 2 (CLL/SLL ≥2 prior regimens including BTK inhibitor)

- In the EAS, among the 263 evaluable patients with CLL/SLL in Cohort 2, the ORR of PR or better by Investigator assessment was 68.4% (180/263; 95% CI: 62.45, 74.01) including a best response of CR in 4 (1.5%) patients and PR in 175 (66.5%) patients.
- PR with lymphocytosis (PR-L) was reported as BOR in 18 (6.8%) patients in Cohort 2, with an ORR including PR-L by Investigator assessment of 75.3% (198/263; 95% CI: 69.61, 80.38).
- The KM estimate of the median DOR by Investigator assessment was 18.40 months (95% CI: 15.64, 20.24) with 107 events observed in 198 responders at a median duration follow-up of 20.4 months. By KM estimate, the probability of remaining in response by Investigator assessment at 12, 15, and 18 months was 69.4% (95% CI: 62.1%, 75.6%), 58.3% (95% CI: 50.6, 65.2), and 51.5% (95% CI: 43.6%, 58.8%), respectively.
- For patients with CLL/SLL in Cohort 2, the median PFS was 19.35 months (95% CI: 16.59, 21.95) by Investigator assessment. By KM estimate, the probability of being progression-free by Investigator assessment at 12, 18, and 24 months was 68.9% (95% CI: 62.8, 74.3), 52.4% (95% CI: 45.8, 58.6), and 37.0% (95% CI: 30.4, 43.7), respectively.
- In Cohort 2, the median OS was not reached (95% CI: 37.13, NE) with 79 (30.0%) deaths observed in 263 patients after a median follow-up of 27.40 months. At 12, 18, and 24 months,

the KM estimate for OS rate was 84.9% (95% CI: 79.9, 88.7), 78.7% (95% CI: 73.1, 83.2), and 72.8% (95% CI: 66.7, 77.9), respectively.

Cohort 7 (including patients with CLL/SLL or NHL not otherwise specified in Cohorts 1 through 6)

- In Cohort 7, the ORR of PR or better by Investigator assessment was 63.2% (12/19; 95% CI: 38.36, 83.71) including 1 CR and 11 PRs. PR-L was reported as BOR in 1 (5.3%) patient in Cohort 7, with an ORR including PR-L by Investigator assessment of 68.4% (13/19; 95% CI: 43.45, 87.42).
- For patients with CLL in Cohort 7, the KM estimate of the median DOR by Investigator assessment was not reached (95% CI: 9.23, NE) with 3 events observed in 13 responders at a median duration follow-up of 18.43 months. By KM analysis, an estimated 91.7% (95% CI: 53.9%, 98.8) and 82.5% (95% CI: 46.1, 95.3) of responders in Cohort 7 were maintaining response by Investigator assessment at 9 months and 12 months, respectively.
- For patients with CLL in Cohort 7, the median PFS was 23.00 months (95% CI: 11.07, NE) by Investigator assessment. By KM estimate, the probability of being progression-free by Investigator assessment at 12, 18, and 24 months was 66.5% (95% CI: 39.9, 83.4), 66.5% (95% CI: 39.9, 83.4), and 47.9% (95% CI: 19.5, 71.8), respectively.
- In Cohort 7, the median OS was not reached (95% CI: NE, NE) with 2 (10.5%) deaths observed in 19 patients after a median follow-up of 25.07 months. At 12, 18, and 24 months, the KM estimate for OS rate was 94.7% (95% CI: 68.1, 99.2), 94.7% (95% CI: 68.1, 99.2), and 85.3% (95% CI: 50.5, 96.4), respectively.

## 2.4.3. Discussion on clinical efficacy

This variation application is mainly based on the efficacy and safety results from Study 20020 to support the use of pirtobrutinib in the treatment of adult patients with CLL who have been previously treated with a BTK inhibitor. Supportive data are provided from the Phase 1/2 Study 18001 in previously treated patients with CLL/SLL or NHL.

## Design and conduct of clinical studies

Study 20020 is a Phase 3, randomized, multicenter, open-label controlled study aiming to evaluate the efficacy and safety of pirtobrutinib in CLL/SLL adult patients previously treated with a BTK inhibitor.

Enrolled patients received either (ratio 1:1) pirtobrutinib (Arm A) or Investigator's choice (Arm B): bendamustine + rituximab (BendaR) or idelalisib and rituximab (IdelaR). Presence of a 17p deletion and previous venetoclax use were chosen as stratification factors, which is considered relevant since both are relevant prognosis factors.

If eligible, patients initially allocated to IdelaR or BendaR could crossover to pirtobrutinib, upon confirmation of disease progression by Independent Review Committee (IRC). The possibility of crossover could hamper the interpretation of efficacy in the control arm. Fifty patients (42.0%) from Arm B crossed over to pirtobrutinib treatment upon IRC-confirmed progression.

The proposed dosing schedule is identical to the one recommended for relapsed or refractory MCL patients and consistent with the recommended phase 2 dose identified in Study 18001.

Throughout study, doses delayed by more than 6 hours were not to be made up and were considered as missed. Based on PK and safety data subsequently accumulated from supportive study 18001 and

as specified in the approved SmPC, a dose should not be taken after a 12-hour delay. Management by dose interruption or reduction was permitted and will be further discussed below.

Comparators were administered consistently with standard CLL/SLL clinical practice but in view of the target population, comparison with an approved BTK inhibitor would have been preferred. This was not possible at time of the study initiation since ibrutinib was the frontline BTK inhibition therapy and acalabrutinib (Calquence) and zanubritinib (Brukinsa) were still in development.

Considering the differences in study treatments used as comparators, the open-label design is acceptable. However, non-blinding will be a limitation, especially when assessing quality of life.

Eligibility criteria are overall acceptable, limiting inclusion to relapsed or refractory patients with CLL previously treated with a BTK inhibitor, consistently with the claimed indication.

As of the data cut-off (DCO) of 29 August 2024, the study was still ongoing. Forty-six (38.7%) in Arm A were still receiving treatment. As did 5 patients (4.2%) in Arm B, which also included 17 patients (14.3%) who had completed their treatment. Treatment discontinuation was more frequent in Arm B, especially for patients treated with BendaR for whom treatment duration was shorter (6 cycles). Main reasons for treatment discontinuation were progressive disease (31.1%), adverse event (21.0%), physician decision (13.4%) and death (6.7%). In Arm A, 3 patients (2.5%) died and treatment discontinuation was mostly due to progression (35.3%) or an adverse event (16%).

Demographics and baseline disease characteristics were overall balanced among treatment arms.

All patients had received at least 1 prior BTK inhibitor (primarily ibrutinib, followed by acalabrutinib and zanubrutinib) and the median number of prior lines of systematic therapy was 3 in both arms. Noncancer medical history was consistent with risk factors associated with age, previous BTK inhibitor therapy, greater susceptibility to infections in CLL patients and metabolism reprogramming in favour of proliferation and survival.

The proportion of patients with a 17p deletion or previous venetoclax use was also balanced between treatment arms: 46.2% in Arm A vs. 44.5% in Arm B and 50.4% for both arms, respectively. Almost all patients had bulky disease (227 of 238 patients, 95.4%) and more than half (166 patients, 69.7%) had a β2-microglobulin level greater than 3.5 mg/L at baseline, reflecting an increased immune response and associated with a poor prognosis.

Regarding other cytogenetic and high-risk features (, TP53 mutation, IGHV mutation status), data were missing in 17.6.% and 21.8% of patients in Arms A and B respectively. The presence of 17p deletion was missing or unknown for 8 patients (6.7%) in Arm A and 7 patients (5.9%) in Arm B (per central laboratory testing), whereas 17p deletion status was required for inclusion. In addition, IGHV status was missing or unknown for 22 patients (18.5%) in Arm A and 26 patients (21.8%) in Arm B. The IGHV "unmutated" mutation status was higher in Arm A (75.6%) than in Arm B (62.2%), suggesting that patients in pirtobrutinib arm could be seen as slightly worse regarding this specific prognostic factor. In contrast, 17p deletion was higher in Arm B (36.1%) than in Arm A (32.8%). Although discrepancies were observed between the study arms in terms of IGHV mutation status and 17p deletion, poor prognostic factors did not meaningfully impact the interpretation of the efficacy results.

Based on the baseline data altogether, the study population is therefore considered as a representative sample of the target population.

Treatments

Pirtobrutinib was administered until progression or unacceptable toxicity and comparators were administered consistently with standard CLL clinical practice. Compliance was high in both treatment arms.

No dose delay was reported in the experimental arm but approximately half of patients in Arm A (57 patients, 49.1%) had at least one dose modification. Dose modifications were mainly dose hold (54 patients, 46.6%), primarily due to an adverse event (42 patients, 36.2%), followed by subject error (12 patients, 10.3%) and inadequate procedures (5 patients, 4.3%). The impact of these dose interruptions on efficacy and safety outcomes was discussed for each patient. For most patients (including those who had either one or more one-day or one or more consecutive dose interruptions), no impact on efficacy responses was reported. A causal relationship between PD and dose interruptions could not be confirmed nor excluded for 4 patients who missed 7 to 22 consecutive doses and developed progressive disease 7 to 60 days later.

Of the 11 patients who had their dose reduced due to an AE by 29 August 2024, 6 presented AE improvement, which supports the updated wording in section 4.2 of the SmPC regarding management of AE by dose reduction. It should be noted that possible impact on efficacy was reported for 2 patients, one with bulky disease and the other with PD reported two months after dose reduction. A deleterious effect of the dose reduction on the efficacy outcome cannot therefore be ruled out, which is consistent with the assessment of the initial MAA and recommendations for dose reduction that were not endorsed at the time given the small sample size and lack of evidence supporting further dose reduction recommendations in the SmPC.

Endpoints

The hypothesis of this study was the superiority of pirtobrutinib over IdelaR or BendaR for the primary and secondary outcomes.

PFS (defined as the time from randomization until the occurrence of documented disease progression by the IRC, per iwCLL 2018 criteria, or death from any cause in the absence of documented PD) was chosen as primary efficacy endpoint, which is supported considering the external review of events and previous CLL trials with BTK inhibitors.

Overall survival (time from randomization until death from any cause) as assessed by investigator was the relevant key secondary endpoint controlled for multiplicity. Investigators' assessment of PFS, ORR, DOR, EFS and time to next treatment (TTNT) were other secondary endpoints. ORR and DOR were also assessed by IRC to further evaluate response to treatment.

Conduct

The protocol has been amended 5 times, the first patient being included on 09 March 2021 under the version 3.0 of global protocol. The presented changes are acceptable as allowing better representation of the target population while ensuring patient safety.

Regarding important protocol deviations, the number of patients concerned was similar between Arms A and B (25 patients [21.0%] and 30 patients [25.2%], respectively), but mostly in patients treated with pirtobrutinib or IdelaR.

The proportions of patients with important protocol deviations were only comparable between arms in terms of safety and informed consent (5.9% vs. 5.0% and 3.4% vs. 4.2%, respectively) as there was an imbalance in the proportion of patients with protocol deviations related to eligibility reported in Arm A (8.4% vs. 1.7% in Arm B) and the proportion of patients with protocol deviations related to study

procedures in Arm B (15.1% vs. 3.4% in Arm A). Given the nature of these deviations, the impact on overall data reliability is considered limited.

## Efficacy data and additional analyses

Efficacy analyses were based on the ITT set, i.e., all randomised patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

As of 29 August 2024, pirtobrutinib monotherapy showed a clinically meaningful increment in IRC-assessed PFS compared to Arm B (HR=0.536; 95% CI: 0.385, 0.746). The median PFS by IRC assessment for Arm A was 13.96 months (95% CI: 11.24, 16.56) and for Arm B was 8.74 months (95% CI: 8.08, 10.38). The median follow-up time for Arm A was 19.35 months (95% CI: 16.66, 22.14) and for Arm B was 17.74 months (95% CI: 13.93, 22.90).

By the August 2024 data cut, the median OS was 29.67 months (95% CI: 27.10, NE) with a median follow-up of 20.37 months. Median OS was not reached in Arm B (median follow-up: 19.22 months). These limited results could be explained by missing/unknown survival data by the new DCO and allowance of crossover as suggested by 3 sensitivity analyses. The CHMP recommended that the MAH submit the final OS results when available.

As of 29 August 2024, the median PFS by Investigator assessment for Arm A was 15.28 months (95% CI: 12.81, 19.94) and for Arm B was 9.20 months (95% CI: 7.33, 10.64). The median follow-up time for Arm A was 19.38 months (95% CI: 16.72, 21.98) and for Arm B was 17.54 months (95% CI: 13.93, 22.90).

Investigator- and IRC-assessed ORR in Arm A were 66.4% (95%CI: 57.15, 74.78) and 48.7% (95% CI: 39.47, 58.07), respectively. A post-hoc analysis for IRC assessments without confirmation of PR or better was performed, showing an ORR comparable to Investigator assessment: 60.5% (95%CI: 51.13, 69.34). Although post-hoc data should be interpreted with caution, those results are supportive. The duration of response was also comparable between investigator and IRC assessment for the pirtobrutinib treated patients:  13.86 months (95% CI: 11.07, 19.12) and 13.77 months (95% CI: 11.07, NE), respectively.

The EFS results in the matured August 2024 data cut showed improvement for pirtobrutinib monotherapy compared to Arm B (HR=0.387; 95% CI: 0.280, 0.534). Median EFS by Investigator assessment was meaningfully longer with pirtobrutinib, at 14.06 months versus 7.62 months for Arm B.

The TTNT results in the matured August 2024 data cut showed improvement in TTNT for pirtobrutinib monotherapy (Arm A) compared to Arm B (HR=0.365; 95% CI: 0.254, 0.524). Median TTNT for pirtobrutinib was 23.95 months (95% CI: 17.84, 29.67) versus 10.91 months (95% CI: 8.74, 12.48) in Arm B.

Crossover to pirtobrutinib was conditioned by a rescreening but eligible patients were not required to observe the rituximab washout period. This approach is endorsed as aiming to limit further disease progression although the potential effect of rituximab and its participation to the response reported in patients who discontinued rituximab upon crossover were questioned. As only 3 of the 50 crossover patients did not observe the washout period (3 to 3.6 weeks between their last infusion of rituximab and the first of pirtobrutinib), the contribution of rituximab to the efficacy response among crossover patients is therefore considered minor.

Interpretability of OS is difficult to assess due to crossover and missing survival data. However, results to date do not indicate a detrimental effect and thus support use of pirtobrutinib in adult patients with CLL who have been previously treated with a Bruton’s tyrosine kinase (BTK) inhibitor.

Patient-reported outcomes

Analysis of PRO endpoints (i.e. Time to sustained worsening (TTSW) of CCL/SLL-related symptoms or physical function) in this study were not controlled for type 1 error.

Time to worsening (TTW) of patient-reported CLL/SLL-related symptoms and TTW of physical functioning (PF) were analysed as secondary endpoints, both descriptive as they were not controlled for the type 1 error. Data from the final analysis of PRO endpoints suggested a favourable trend for pirtobrutinib in terms of PF, but no significant difference was reported for CLL/SLL-related symptoms. Due to the pre-specified censoring design and the decreasing number of PRO questionnaires completed throughout study, the median was not reached for either endpoint.

TTW of patient-reported CLL/SLL-related symptoms and TTW of PF were also assessed as exploratory endpoints using the Mixed Models for Repeated Measures . While results from the February 2024 data cut suggest a favourable trend for pirtobrutinib for both endpoints, data beyond this date are inconclusive due to lack of randomization.

Although these updated PRO are difficult to interpret due to the short-time follow-up, some improvements in terms of CLL/SLL-related symptoms and PF were reported at some timepoints beyond Week 25, providing overall support for the suitability of pirtobrutinib treatment in the claimed indication.

Additional analyses

Sensitivity analyses of PFS based on IRC assessments were performed.

A trend in favour of pirtobrutinib treatment is observed in PFS subgroup by disease characteristics. However, confidence intervals are large and a sample size effect cannot be ruled out. No clear conclusion could be drawn given the absence of statistical significance for the majority of the effects observed.

Sensitivity analyses were also planned for OS but not discussed given the immaturity of presented data by the data cut-off date.

**Supportive study**

Interim results from Phase 1/2 Study 18001, a multicenter Phase 1/2 study aimed to evaluate safety and efficacy of oral pirtobrutinib in heavily pre-treated patients with CLL/SLL or B-cell NHL who have failed or were intolerant to standard of care.

At the time of the interim analysis, 263 patients with CLL/SLL previously treated with a BTK inhibitor (Cohort 2) were evaluable for analysis of overall response. In Cohort 7, all 28 patients with MCL and all 19 patients with CLL/SLL were evaluable for analysis of overall response.

Overall, interim efficacy results from supportive Study 18001 provided longer-term data suggesting a sustained treatment effect of pirtobrutinib treatment in a larger study sample based on efficacy parameters by Investigator. However, the population studied slightly differs from the target population being heavily pretreated, therefore those non-comparative and immature results were not included in the SmPC.

Overall, Study 20020 which included relapsed or refractory CLL patients previously treated with a BTK inhibitor. The study population adequately reflects the intended target population and is well-designed.

As CLL and SLL are considered distinct clinical manifestations of the same biologic disease by the World Health Organization (WHO) classification the indication was revised to only refer to CLL.

## 2.4.4. Conclusions on the clinical efficacy

Results from the pivotal study indicate that pirtobrutinib has a clinically meaningful impact on PFS and therefore support the indication Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor.

## *2.5. Clinical safety*

### *Introduction*

Pirtobrutinib as monotherapy is indicated since October 2023 in Europe for the treatment of adult patients with relapsed or refractory MCL who have been previously treated with a BTK inhibitor.

The most common adverse reactions for pirtobrutinib listed in the EU SmPC are neutropenia, thrombocytopenia, anaemia, haemorrhage, bruising, contusion, diarrhoea, abdominal pain, nausea, rash, arthralgia and fatigue.

The primary safety data for this extension of indication application comes from an analysis of patients on pivotal study 20020, comparing the efficacy and safety of pirtobrutinib 200 mg once daily (QD) as monotherapy (Safety Population, Arm A; n = 116) to Investigator's choice of either idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BendaR) (Safety Population Arm B; n = 109) in CLL/SLL patients previously treated with a BTK inhibitor.

Supportive safety data comes from patients in Study 18001 irrespective of B-cell malignancy, who received at least 1 dose of pirtobrutinib as monotherapy at a starting dose of 200 mg QD without subsequent dose escalation (OMTSAS-200; n = 588). Safety data from a subgroup patient population with CLL/SLL (CSAS-200; n = 220) is also included.

### *Patient exposure*

#### *Study 20020*

This study included 238 patients with CLL previously treated with any BTK inhibitor who had an indication for treatment as defined by iwCLL 2018 criteria (Hallek et al. 2018), including those who discontinued prior covalent BTK therapy due to progressive disease (PD) or intolerance. Eligible patients were randomised 1:1 into Arm A and Arm B and were stratified by deletion 17p presence (yes/no) and by prior venetoclax treatment (yes/no). Patients in Arm B were allowed to cross over to Arm A upon experiencing Independent Review Committee-confirmed PD and meeting crossover eligibility criteria.

Study 20020 is currently ongoing.

The median duration on therapy for patients who received pirtobrutinib in Arm A was 15.05 (range: 0.10 to 33.41) months. The median duration on therapy for patients in the IdelaR treatment group was 7.08 (range: 0.30 to 29.01) months for idelalisib and 5.49 (range: 0.92 to 6.90) months for rituximab. The median duration on therapy for patients in the BendaR treatment group was 4.73 (range: 0.92 to 12.19) months for bendamustine and 4.70 (range: 0.92 to 12.16) months for rituximab.

The MAH submitted data with 2 cut-off dates for this study: August 2023 and August 2024. Data in this section are from the August 2024 cut-off date unless otherwise specified.

***Study 18001***

Supportive safety data for this SCS comes from an interim analysis of Phase 1 and Phase 2 monotherapy data from Study 18001 with a data cut of 05 May 2023. Safety data from patients who received pirtobrutinib monotherapy at a starting dose of 200 mg QD without subsequent dose escalation (OMTSAS-200 and CSAS-200) were used in the safety analysis.

The first patient in Study 18001 was enrolled in March 2019 and the study is ongoing; Study 18001 was closed for enrolment on 20 January 2023. Patients were treated at pirtobrutinib doses ranging from 25 mg QD through 300 mg QD during Phase 1. Safety and efficacy findings were described in the interim Study 18001 CSR. The approved dose is 200 mg QD for the MCL and CLL indications (JAYPIRCA, USPI; JAYPIRCA, SmPC).

The median time on pirtobrutinib treatment was higher for both OMTSAS-200 and CSAS-200 from Study 18001 (10.15 months and 20.63 months, respectively) compared to the median time on pirtobrutinib for patients in Study 20020 Arm A.

The MAH submitted data with 2 cut-off dates for this study: May 2023 and January 2024. Data in this section are from the January 2024 cut-off date unless otherwise specified.

## *Adverse events*

***Study 20020***

In Study 20020 Arm A, the majority of patients experienced at least one AE (108 [93.1%]). Grade 3 or 4 AEs occurred in 55 (47.4%) patients. Treatment-related AEs occurred in 71 (61.2%) patients. SAEs occurred in 55 (47.4%) patients. There were 20 (17.2%) patients who discontinued pirtobrutinib due to an AE; 6 (5.2%) patients discontinued pirtobrutinib due to a treatment-related AE. Nine (7.8%) patients had a fatal AE.

In Study 20020 Arm B, the majority (107 [98.2%]) of patients experienced at least one AE. Grade 3 or 4 AEs occurred in 70 (64.2%) of patients. Treatment-related AEs occurred in 90 (82.6%) patients. SAEs were reported in 51 (46.8%) patients. Thirty-eight (34.9%) patients discontinued any study treatment due to an AE; 23 patients (21.1%) discontinued any study treatment due to AEs related to study treatment. Seven (6.4%) patients had a fatal AE.

The most common AEs are summarised in **Table 25**.

**Table 25.** Treatment-Emergent Adverse Events by PT and Maximum Severity in ≥ 15% of Patients in Arm A or Arm B by Decreasing Frequency.

| | **Arm A Pirtobrutinib (N=116)** | | **Arm B IdelaR or BendaR (N=109)** | |
|---|---|---|---|---|
| TEAE | **Any grade n (%)** | **Grade 3+ n (%)** | **Any grade n (%)** | **Grade 3+ n (%)** |
| Subjects with ≥1 TEAE | 108 (93.1) | 67 (57.8) | 107 (98.2) | 80 (73.4) |
| Pneumonia | 26 (22.4) | 20 (17.2) | 13 (11.9) | 12 (11.0) |
| Anaemia | 23 (19.8) | 13 (11.2) | 19 (17.4) | 8 (7.3) |
| Neutropenia | 21 (18.1) | 17 (14.7) | 17 (15.6) | 13 (11.9) |

| TEAE | Arm A Pirtobrutinib (N=116) | | Arm B IdelaR or BendaR (N=109) | |
|---|---|---|---|---|
| | Any grade n (%) | Grade 3+ n (%) | Any grade n (%) | Grade 3+ n (%) |
| Cough | 19 (16.4) | 0 | 19 (17.4) | 0 |
| Diarrhoea | 19 (16.4) | 0 | 34 (31.2) | 6 (5.5) |
| COVID-19 | 15 (12.9) | 2 (1.7) | 20 (18.3) | 5 (4.6) |
| Pyrexia | 15 (12.9) | 1 (0.9) | 29 (26.6) | 1 (0.9) |
| Fatigue | 13 (11.2) | 2 (1.7) | 22 (20.2) | 1 (0.9) |
| Nausea | 13 (11.2) | 1 (0.9) | 22 (20.2) | 0 |
| Neutrophil count decreased | 9 (7.8) | 6 (5.2) | 19 (17.4) | 14 (12.8) |
| Vomiting | 8 (6.9) | 1 (0.9) | 19 (17.4) | 0 |
| ALT increased | 4 (3.4) | 1 (0.9) | 19 (17.4) | 10 (9.2) |
| Weight decreased | 4 (3.4) | 0 | 18 (16.5) | 0 |
| Infusion related reaction | 0 | 0 | 19 (17.4) | 3 (2.8) |

*Abbreviations: ALT = alanine aminotransferase; n = number of patients; N = number of patients in treatment group; TEAE = treatment-emergent adverse event.*

The incidence rate per 100 patient-years of TEAEs by PT occurring in ≥ 5% of patients is shown in **Table 26**.

**Table 26**. TAE by PT in ≥5% of patients with exposure-adjusted incidence rates in order of decreasing incidence rate in Arm A

| | August 2023 Data Cut | | | | | | August 2024 Data Cut | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm A (N=116, PY[a]=87.6) | | | Arm B (N=109, PY=56.9) | | | Arm A (N=116, PY[a]=146.6) | | | Arm B (N=109, PY=69.7) | | |
| MedDRA PT | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] |
| | | | | | | | | | | | | |
| Anaemia | 21 | 71.2 | 29.5 | 18 | 52.3 | 34.4 | 23 | 124.5 | 18.5 | 19 | 62.8 | 30.3 |
| Neutropenia | 19 | 78.7 | 24.1 | 15 | 51.0 | 29.4 | 21 | 129.6 | 16.2 | 17 | 62.5 | 27.2 |
| Pneumonia | 18 | 77.9 | 23.1 | 9 | 55.3 | 16.3 | 26 | 127.5 | 20.4 | 13 | 66.6 | 19.5 |
| Diarrhoea | 16 | 77.9 | 20.6 | 26 | 45.9 | 56.7 | 19 | 124.5 | 15.3 | 34 | 53.4 | 63.7 |
| Oedema peripheral | 12 | 77.6 | 15.5 | 6 | 55.4 | 10.8 | 13 | 130.6 | 10.0 | 7 | 67.2 | 10.4 |
| Pyrexia | 13 | 80.5 | 16.2 | 26 | 47.9 | 54.3 | 15 | 134.8 | 11.1 | 29 | 55.4 | 52.4 |
| Headache | 11 | 80.0 | 13.8 | 15 | 49.9 | 30.1 | 13 | 128.8 | 10.1 | 16 | 61.0 | 26.2 |
| COVID-19 | 11 | 81.4 | 13.5 | 19 | 49.2 | 38.6 | 15 | 134.6 | 11.1 | 20 | 59.9 | 33.4 |
| Nausea | 11 | 79.7 | 13.8 | 22 | 48.5 | 45.4 | 13 | 132.2 | 9.8 | 22 | 57.4 | 38.3 |
| Rash | 10 | 79.6 | 12.6 | 8 | 54.2 | 14.8 | 11 | 134.0 | 8.2 | 9 | 65.4 | 13.8 |
| Fatigue | 9 | 82.6 | 10.9 | 15 | 53.2 | 28.2 | 13 | 136.7 | 9.5 | 22 | 64.3 | 34.2 |
| Cough | 9 | 83.7 | 10.8 | 15 | 52.2 | 28.7 | 19 | 132.5 | 14.3 | 19 | 61.7 | 30.8 |
| Thrombocytopenia | 8 | 84.5 | 9.5 | 8 | 55.5 | 14.4 | 10 | 142.1 | 7.0 | 8 | 67.8 | 11.8 |
| Neutrophil count decrease | 8 | 81.7 | 9.8 | 17 | 51.7 | 32.9 | 9 | 135.7 | 6.6 | 19 | 63.1 | 30.1 |
| Asthenia | 7 | 83.0 | 8.4 | 4 | 54.4 | 7.4 | 9 | 139.4 | 6.5 | 5 | 65.3 | 7.7 |
| Hypertension | 7 | 84.9 | 8.2 | 4 | 54.4 | 7.4 | 8 | 138.3 | 5.8 | 4 | 65.4 | 6.1 |
| Hyperkalaemia | 6 | 84.2 | 7.1 | 4 | 53.1 | 7.5 | 7 | 139.8 | 5.0 | 4 | 65.2 | 6.1 |
| Upper respiratory tract infection | 7 | 81.6 | 8.6 | 5 | 54.2 | 9.2 | 12 | 132.8 | 9.0 | 7 | 66.9 | 10.5 |
| Back pain | 6 | 82.9 | 7.2 | 4 | 55.5 | 7.2 | 11 | 136.4 | 8.2 | 5 | 68.2 | 7.3 |
| Vomiting | 6 | 84.2 | 7.1 | 16 | 52.7 | 30.4 | 8 | 139.0 | 5.8 | 19 | 64.1 | 29.6 |
| Constipation | 6 | 83.8 | 7.2 | 10 | 53.6 | 18.6 | 7 | 138.7 | 5.0 | 12 | 66.1 | 18.2 |
| Arthralgia | 6 | 84.5 | 7.1 | 8 | 52.1 | 15.4 | 9 | 139.8 | 6.4 | 8 | 63.3 | 12.6 |

Abbreviations: IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; PYE = patient-years of exposure; TEAEs = treatment-emergent adverse events.

[a] PY is the sum of the years for the TEAE observation periods across all patients

[b] PYE is the sum of the years at risk for a TEAE across all patients, defined from treatment start date until date of first occurrence of the TEAE or end of analysis period for patients with or without the TEAE, respectively

[c] IR is for the first occurrence of the event and is calculated as n divided by PYE times 100.

The incidence rate of Grade 3 and 4 events occurring in ≥ 5 patients, per 100 patient-years, are shown in **Table 27**.

**Table 27.** Grade 3/4 TEAE by PT and maximum severity in ≥5 patients with exposure-adjusted incidence rates in order of decreasing incidence rate in Arm A

| | August 2023 Data Cut | | | | | | August 2024 Data Cut | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm A (N=116, PY[a]=87.6) | | | Arm B (N=109, PY=56.9) | | | Arm A (N=116, PY[a]=146.6) | | | Arm B (N=109, PY=69.7) | | |
| MedDRA PT | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] | n | PYE[b] | IR[c] |
| Neutropenia | 15 | 81.7 | 18.4 | 12 | 53.0 | 22.6 | 17 | 135.8 | 12.5 | 13 | 65.2 | 19.9 |
| Pneumonia | 14 | 79.8 | 17.5 | 5 | 56.0 | 8.9 | 18 | 131.8 | 13.7 | 9 | 67.0 | 13.4 |
| Anaemia | 12 | 78.3 | 15.3 | 6 | 55.6 | 10.8 | 13 | 134.6 | 9.7 | 8 | 67.7 | 11.8 |
| Thrombocytopenia | 6 | 85.6 | 7.0 | 4 | 56.5 | 7.1 | 8 | 143.1 | 5.6 | 5 | 68.7 | 7.3 |
| Neutrophil count decreased | 5 | 83.7 | 6.0 | 13 | 52.7 | 24.7 | 6 | 140.0 | 4.3 | 14 | 64.5 | 21.7 |

Abbreviations: IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; PY = patient-years; PYE = patient-years of exposure; TEAEs = treatment-emergent adverse events.

[a] PY is the sum of the years for the TEAE observation periods across all patients.

[b] PYE is the sum of the years at risk for a TEAE across all patients, defined from treatment start date until date of first occurrence of the TEAE or end of analysis period for patients with or without the TEAE, respectively.

[c] IR is for the first occurrence of the event and is calculated as n divided by PYE times 100.

***Study 18001***

In Study 18001 OMTSAS-200, 550 (95.8%) patients experienced at least one AE and 319 (55.6%) patients experienced Grade 3 or 4 AEs. Treatment-related AEs occurred in 364 (63.4%) patients. SAEs were reported in 272 patients (47.4%). There were 63 (11%) patients who discontinued pirtobrutinib due to an AE. There were 47 (8.2%) patients who experienced a fatal AE.

In the Study 18001 OMTSAS-200, the most common AEs (occurring in ≥ 15% of patients) were fatigue, diarrhoea, COVID-19, contusion, anaemia, cough, dyspnoea, nausea, neutrophil count decreased, and arthralgia.

The number of AEs that occurred in ≥ 15% of patients was higher in Study 18001 OMTSAS-200 than in Arm A of Study 20020. The difference can be explained by the longer follow-up in Study 18001 OMTSAS-200. The most common AEs reported in Study 18001 OMTSAS-200 were similar to those that were reported in patients from Study 20020 Arm A.

## *Serious adverse event/deaths/other significant events*

***Serious adverse events***

*Study 20020*

The incidence of SAEs was similar between arms. SAEs occurred in 55 (47.4%) pirtobrutinib-treated patients (Arm A) compared to 51 (46.8%) patients in Arm B, (**Table 28**).

**Table 28**. Treatment-Emergent Serious Adverse Events by Maximum Severity in >2% of Patients in Either Arm – Safety Population

| TESAE, n (%) | Arm A<br>Pirtobrutinib<br>(N=116) | Arm B<br>IdelaR or BendaR<br>(N=109) |
|---|---|---|
| Subjects with ≥1 TESAE | 55 (47.4) | 51 (46.8) |
| Pneumonia | 18 (15.5) | 12 (11.0) |
| COVID-19 Pneumonia | 4 (3.4) | 3 (2.8) |
| Anaemia | 3 (2.6) | 2 (1.8) |
| COVID-19 | 2 (1.7) | 5 (4.6) |
| Pyrexia | 2 (1.7) | 3 (2.8) |
| Febrile Neutropenia | 0 | 4 (3.7) |
| Diarrhoea | 0 | 4 (3.7) |
| Infusion related reaction | 0 | 3 (2.8) |

*Abbreviations: n = number of patients; N = number of patients in treatment group; TESAE = treatment emergent serious adverse event.*

*Study 18001*

**Table 29.** Serious Adverse Events Occurring in ≥1% of Patients by Preferred Term in Order of Decreasing Incidence in OMTSAS 200

| PT, n (%) | Study 18001 (Jan24) | |
|---|---|---|
| | CSAS-200<br>(N=212) | OMTSAS-200<br>(N=574) |
| | All | All |
| Any SAE | 123 (58.0) | 272 (47.4) |
| Pneumonia | 17 (8.0) | 37 (6.4) |
| COVID-19 pneumonia | 21 (9.9) | 37 (6.4) |
| COVID-19 | 13 (6.1) | 19 (3.3) |
| Febrile neutropenia | 10 (4.7) | 16 (2.8) |
| Sepsis | 5 (2.4) | 15 (2.6) |
| Anaemia | 10 (4.7) | 15 (2.6) |
| Acute kidney injury | 5 (2.4) | 11 (1.9) |
| Pyrexia | 2 (0.9) | 9 (1.6) |
| Dyspnoea | 5 (2.4) | 8 (1.4) |
| Respiratory failure | 5 (2.4) | 9 (1.6) |
| Atrial fibrillation | 4 (1.9) | 8 (1.4) |
| Bacteraemia | 2 (0.9) | 6 (1.0) |
| Septic Shock | 5 (2.4) | 6 (1.0) |
| Urinary tract infection | 3 (1.4) | 6 (1.0) |

*Abbreviations: COVID-19 = coronavirus disease 2019; CSAS-200 = CLL safety analysis set; ISS = integrated safety set; OMTSAS-200 = overall monotherapy safety analysis set; PT = preferred term; SAE = serious adverse event.*

***Deaths***

*Study 20020*

In Arm A, 37 (31.9%) of 116 patients in the safety population, died on or before the 29 August 2024 data cutoff; of note, one additional patient died in the ITT population before receiving first dose of pirtobrutinib, this case does not belong to safety population as the patient was not exposed to pirtobrutinib. Of the 37 patients who received at least one dose of pirtobrutinib in Arm A, 17 deaths were due to progressive disease, 15 deaths were due to adverse events and 5 were deaths due to other reasons (2 deterioration in general health, 3 unknown); No patients died on therapy, 9 (7.8%) died within 30 days of the last study drug dose and the remaining after 30 days of last dose. None of the deaths in Arm A patients were considered related to pirtobrutinib by the investigator. In Arm B, 22 (20.2%) of 109 patients in the safety population died on or before the 29 August 2024 data cutoff; no patients died on therapy and 9 (8.3%) died within 30 days of the last study drug dose (IdelaR: 7 [9.1%] patients; BendaR: 2 [6.3%] patients).

In both Arm A and Arm B, the most common reason for death within 30 days of the last study drug dose was an adverse event (Arm A: 9 [7.8%] patients; Arm B: 7 [6.4%] patients) most commonly due to COVID-19 pneumonia in Arm A (3 patients, 2.6%) and pneumonia in Arm B (2 patients, 1.8%).

*Study 18001*

The reported cases with a fatal outcome in Study 18001 are summarised in **Table 30**.

**Table 30.** Summary of Deaths – Study 18001 (May 2023 data cut-off)

| | CSAS-200 (N=220) | OMTSAS-200 (N=588) |
|---|---|---|
| **Subjects with any Serious TEAEs with Fatal Outcome** | 25 (11.4) | 44 (7.5) |
| COVID-19 pneumonia | 4 (1.8) | 8 (1.4) |
| COVID-19 | 5 (2.3) | 5 (0.9) |
| Respiratory failure | 2 (0.9) | 5 (0.9) |
| Septic shock | 2 (0.9) | 3 (0.5) |
| Cardiac arrest | 0 | 2 (0.3) |
| Sepsis | 2 (0.9) | 2 (0.3) |
| Bacterial sepsis | 0 | 1 (0.2) |
| Cerebrovascular accident | 1 (0.5) | 1 (0.2) |
| Escherichia sepsis | 1 (0.5) | 1 (0.2) |
| Haemorrhage | 0 | 1 (0.2) |
| Haemorrhage intracranial | 0 | 1 (0.2) |
| Infectious pleural effusion | 1 (0.5) | 1 (0.2) |
| Malignant pleural effusion | 0 | 1 (0.2) |
| Metastatic malignant melanoma | 1 (0.5) | 1 (0.2) |
| Mucormycosis | 0 | 1 (0.2) |
| Multiple organ dysfunction syndrome | 0 | 1 (0.2) |
| Pneumonia | 1 (0.5) | 1 (0.2) |
| Pneumonia fungal | 1 (0.5) | 1 (0.2) |
| Pneumonia legionella | 1 (0.5) | 1 (0.2) |
| Pulmonary embolism | 0 | 1 (0.2) |
| Shock | 1 (0.5) | 1 (0.2) |
| Splenic rupture | 1 (0.5) | 1 (0.2) |
| Streptococcal infection | 0 | 1 (0.2) |
| Sudden death | 0 | 1 (0.2) |
| Transitional cell carcinoma | 1 (0.5) | 1 (0.2) |

There were 3 additional deaths due to AE within 28 days of last dose in Study 18001 (OMTSAS-200) reported during the follow-up period for this safety update compared with the initial submission.

The AEs reported in these cases, and which were considered not related to pirtobrutinib were respiratory failure, headache and urinary tract infection.

***Adverse events of special interest***

*Study 20020*

The adverse events of special interest reported in study 20020 are summarised in **Table 31**.

**Table 31**. Summary of Treatment-Emergent Adverse Events of Special Interest by Special Interest - Safety Population

| AESI, n (%) | Arm A Pirtobrutinib N=116 | | Arm B IdelaR or BendaR N=109 | |
|---|---|---|---|---|
| | **Any grade** | **Grade 3+** | **Any grade** | **Grade 3+** |
| Subjects with ≥1 AESI | 85 (73.3) | 54 (46.6) | 76 (69.7) | 51 (46.8) |
| Bleeding | 25 (21.6) | 4 (3.4) | 11 (10.1) | 1 (0.9) |
| Anaemia | 24 (20.7) | 13 (11.2) | 19 (17.4) | 8 (7.3) |
| Neutropenia | 31 (26.7) | 24 (20.7) | 37 (33.9) | 30 (27.5) |
| Thrombocytopenia | 11 (9.5) | 9 (7.8) | 17 (15.6) | 8 (7.3) |
| Infection | 74 (63.8) | 34 (29.3) | 54 (49.5) | 26 (23.9) |
| Infection without COVID-19 | 67 (57.8) | 30 (25.9) | 47 (43.1) | 22 (20.2) |
| Atrial fibrillation and atrial flutter | 3 (2.6) | 2 (1.7) | 1 (0.9) | 0 |

*Abbreviations: AESI = adverse events of special interest; n = number of patients; N = number of patients in treatment group.*

*Study 18001*

The adverse events of special interest reported in study 18001 are summarised in **Table 32**.

**Table 32.** Summary of Adverse Events of Special Interest

| Composite term, n (%) | Study 18001 (Jan24) CSAS-200 (N=212) | Study 18001 (Jan24) OMTSAS-200 (N=574) |
|---|---|---|
| **Infection (including COVID-19)** | | |
| Any grade | 152 (71.7) | 336 (58.5) |
| Grade 3 or 4 | 56 (26.4) | 123 (21.4) |
| Grade 5 | 19 (9.0) | 27 (4.7) |
| **Infection (excluding COVID-19** | | |
| Any grade | 127 (59.9) | 289 (50.3) |
| Grade 3 or 4 | 38 (17.9) | 95 (16.6) |
| Grade 5 | 10 (4.7) | 14 (2.4) |
| **Bleeding** | | |
| Any grade | 97 (45.8) | 224 (39.0) |
| Grade 3 or 4 | 5 (2.4) | 15 (2.6) |
| Grade 5 | 0 | 2 (0.3) |
| **Bruising** | | |

| Composite term, n (%) | Study 18001 (Jan24) | |
|---|---|---|
| | CSAS-200 (N=212) | OMTSAS-200 (N=574) |
| Any grade | 59 (27.8) | 127 (22.1) |
| Grade 3 or 4 | 0 | 1 (0.2) |
| **Haemorrhage** | | |
| Any grade | 53 (25.0) | 122 (21.3) |
| Grade 3 or 4 | 5 (2.4) | 14 (2.4) |
| Grade 5 | 0 | 2 (0.3) |
| **Petechia and Purpura** | | |
| Any grade | 18 (8.5) | 40 (7.0) |
| Grade 3 or 4 | 0 | 0 |
| **Neutropenia** | | |
| Any grade | 81 (38.2) | 160 (27.9) |
| Grade 3 or 4 | 71 (33.5) | 141 (24.6) |
| **Anaemia** | | |
| Any grade | 48 (22.6) | 119 (20.7) |
| Grade 3 or 4 | 24 (11.3) | 64 (11.1) |
| **Thrombocytopenia** | | |
| Any grade | 43 (20.3) | 105 (18.3) |
| Grade 3 or 4 | 24 (11.3) | 58 (10.1) |
| **Atrial fibrillation/flutter** | | |
| Any grade | 12 (5.7) | 23 (4.0) |
| Grade 3 or 4 | 5 (2.4) | 10 (1.7) |

*Abbreviations: AESI = adverse event of special interest; CLL = chronic lymphocytic leukaemia; CSAS-200 = CLL safety analysis set; ISS = integrated safety set; n = number of subjects in the specified category; N = number of subjects in integrated safety population; OMTSAS-200 = overall monotherapy safety analysis set.*

***Adverse Events of Potential Clinical Significance***

*Study 20020*

The AEPCS reported in the Study 20020 Arm A are summarised in **Table 33** .

**Table 33.** Summary of Adverse Events of Potential Clinical Significance - Safety Population

| AEPCS, n (%) | Arm A Pirtobrutinib N=116 | | Arm B IdelaR or BendaR N=109 | |
|---|---|---|---|---|
| | Any grade | Grade 3+ | Any grade | Grade 3+ |
| Subjects with ≥1 AEPCS | 39 (33.6) | 14 (12.1) | 34 (31.2) | 11 (10.1) |

| AEPCS, n (%) | Arm A Pirtobrutinib N=116 | | Arm B IdelaR or BendaR N=109 | |
|---|---|---|---|---|
| Rash | 19 (16.4) | 3 (2.6) | 21 (19.3) | 5 (4.6) |
| Lymphocytosis | 9 (7.8) | 5 (4.3) | 4 (3.7) | 3 (2.8) |
| Cardiac Failure | 3 (2.6) | 3 (2.6) | 0 | 0 |
| Hypertension | 8 (6.9) | 3 (2.6) | 5 (4.6) | 2 (1.8) |
| Second Primary Malignancy | 8 (6.9) | 2 (1.7) | 2 (1.8) | 1 (0.9) |
| Second Primary Malignancy Non-melanoma Skin Cancer | 4 (3.4) | 2 (1.7) | 1 (0.9) | 0 |
| Second Primary Malignancy excluding Non-melanoma Skin Cancer | 4 (3.4) | 0 | 1 (0.9) | 1 (0.9) |
| Tumour Lysis Syndrome | 1 (0.9) | 1 (0.9) | 0 | 0 |
| Supraventricular Tachyarrhythmias excluding Atrial Fibrillation and Atrial Flutter | 0 | 0 | 3 (2.8) | 0 |

*Abbreviations: AEPCS = adverse events of potential clinical significance; n = number of patients; N = number of patients in treatment group.*

*Study 18001*

The AEPCS reported in the Study 18001 Arm A are summarised in **Table 34**.

**Table 34**. Summary of Treatment-Emergent Adverse Events of Potential Clinical Significance

| n (%) | Study 18001 (Jan24) | |
|---|---|---|
| | CSAS-200 (N=212) | OMTSAS-200 (N=574) |
| **Rash**[a] | | |
| Any grade | 49 (23.1) | 108 (18.8) |
| Grade 3 or 4 | 2 (0.9) | 5 (0.9) |
| **Cardiovascular events** | | |
| **Hypertension**[a] | | |
| Any grade | 39 (18.4) | 68 (11.8) |
| Grade 3 or 4 | 18 (8.5) | 27 (4.7) |
| **Heart failure**[a] | | |
| Any grade | 7 (3.3) | 10 (1.7) |
| Grade 3 or 4 | 5 (2.4) | 6 (1.0) |
| **Ventricular tachyarrhythmias**[a] | | |
| Any grade | 4 (1.9) | 7 (1.2) |

| n (%) | Study 18001 (Jan24) | |
|---|---|---|
| | **CSAS-200 (N=212)** | **OMTSAS-200 (N=574)** |
| Grade 3 or 4 | 0 | 0 |
| **Supraventricular tachyarrhythmias**[a,b] | | |
| Any grade | 14 (6.6) | 28 (4.9) |
| Grade 3 or 4 | 3 (1.4) | 5 (0.9) |
| **Second primary malignancy** | | |
| Any grade | 38 (17.9) | 57 (9.9) |
| Grade 3 or 4 | 10 (4.7) | 18 (3.1) |
| Grade 5 | 2 (0.9) | 2 (0.3) |
| **Second primary malignancy: non-melanoma skin cancer**[a] | | |
| Any grade | 16 (7.5) | 25 (4.4) |
| Grade 3 or 4 | 1 (0.5) | 3 (0.5) |
| **Second primary malignancy: excluding non-melanoma skin cancer** | | |
| Any grade | 25 (11.8) | 36 (6.3) |
| Grade 3 or 4 | 9 (4.2) | 16 (2.8) |
| Grade 5 | 2 (0.9) | 2 (0.3) |
| **Lymphocytosis**[a] | | |
| Any grade | 20 (9.4) | 35 (6.1) |
| Grade 3 or 4 | 13 (6.1) | 22 (3.8) |
| **TLS**[a] | | |
| Any grade | 1 (0.5) | 4 (0.7) |
| Grade 3 or 4 | 1 (0.5) | 4 (0.7) |

*Abbreviations: AEs = adverse events; AEPCS = adverse events of potential clinical significance; CLL = chronic lymphocytic leukaemia; CSAS-200 = CLL safety analysis set; ISS = integrated safety set; n = number of subjects in the specified category; N = number of subjects in integrated safety population; OMTSAS-200 = overall monotherapy safety analysis set; TLS = tumour lysis syndrome.*

[a] *No Grade 5 AEPCS were reported.*

[b] *Supraventricular tachyarrhythmias excludes AEs of atrial fibrillation and atrial flutter.*

## *Laboratory findings*

### *Haematology*

Analyses of haematology lab values (**Table 35**) were consistent with analyses of the haematological AEs described in in the adverse events sections of this report.

Overall, on-treatment hematologic laboratory post-baseline shifts were generally transient, with ultimate recovery at the last post-baseline value recorded.

**Table 35.** Subject Incidence of Treatment-Emergent Abnormal Haematology Laboratory Tests per CTCAE 5.0 Toxicity Grade (Data cutoff: August 2023)

| | | Arm A Pirtobrutinib (N=116) Worst post-baseline grade n(%) | | | | |
|---|---|---|---|---|---|---|
| Lab Parameter | n | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hemoglobin Increased | 114 | 4 ( 3.5) | 4 ( 3.5) | 0 | 0 | 0 |
| Hemoglobin Decreased | 114 | 49 (43.0) | 15 (13.2) | 23 (20.2) | 11 ( 9.6) | 0 |
| Platelets Decreased | 114 | 31 (27.2) | 11 ( 9.6) | 8 ( 7.0) | 6 ( 5.3) | 6 ( 5.3) |
| Leukocytes Increased | 114 | 20 (17.5) | 0 | 0 | 20 (17.5) | 0 |
| Leukocytes Decreased | 114 | 14 (12.3) | 6 ( 5.3) | 3 ( 2.6) | 4 ( 3.5) | 1 ( 0.9) |
| Neutrophils Decreased | 114 | 55 (48.2) | 10 ( 8.8) | 19 (16.7) | 15 (13.2) | 11 ( 9.6) |
| Lymphocytes Increased | 112 | 36 (32.1) | 0 | 11 ( 9.8) | 25 (22.3) | 0 |
| Lymphocytes Decreased | 112 | 9 ( 8.0) | 4 ( 3.6) | 3 ( 2.7) | 2 ( 1.8) | 0 |
| | | Arm B IdelaR (N=77) | | | | |
| Hemoglobin Increased | 75 | 1 ( 1.3) | 1 ( 1.3) | 0 | 0 | 0 |
| Hemoglobin Decreased | 75 | 29 (38.7) | 13 (17.3) | 10 (13.3) | 6 ( 8.0) | 0 |
| Platelets Decreased | 75 | 24 (32.0) | 12 (16.0) | 7 ( 9.3) | 1 ( 1.3) | 4 ( 5.3) |
| Leukocytes Increased | 75 | 5 ( 6.7) | 0 | 0 | 5 ( 6.7) | 0 |
| Leukocytes Decreased | 75 | 18 (24.0) | 8 (10.7) | 7 ( 9.3) | 1 ( 1.3) | 2 ( 2.7) |
| Neutrophils Decreased | 75 | 51 (68.0) | 11 (14.7) | 19 (25.3) | 4 ( 5.3) | 17 (22.7) |
| Lymphocytes Increased | 75 | 22 (29.3) | 0 | 5 ( 6.7) | 17 (22.7) | 0 |
| Lymphocytes Decreased | 75 | 8 (10.7) | 1 ( 1.3) | 3 ( 4.0) | 4 ( 5.3) | 0 |
| | | Arm B BendaR (N=32) | | | | |
| Hemoglobin Increased | 31 | 1 ( 3.2) | 1 ( 3.2) | 0 | 0 | 0 |
| Hemoglobin Decreased | 31 | 14 (45.2) | 8 (25.8) | 4 (12.9) | 2 ( 6.5) | 0 |
| Platelets Decreased | 31 | 18 (58.1) | 10 (32.3) | 6 (19.4) | 1 ( 3.2) | 1 ( 3.2) |
| Leukocytes Increased | 31 | 0 | 0 | 0 | 0 | 0 |
| Leukocytes Decreased | 31 | 14 (45.2) | 2 ( 6.5) | 9 (29.0) | 3 ( 9.7) | 0 |
| Neutrophils Decreased | 31 | 16 (51.6) | 5 (16.1) | 5 (16.1) | 5 (16.1) | 1 ( 3.2) |
| Lymphocytes Increased | 31 | 2 ( 6.5) | 0 | 0 | 2 ( 6.5) | 0 |
| Lymphocytes Decreased | 31 | 11 (35.5) | 0 | 2 ( 6.5) | 7 (22.6) | 2 ( 6.5) |

### *Chemistry*

In general, analyses of serum chemistry lab values (**Table 36**) were consistent with analyses of AE data and did not reveal any additional safety signals in Study 20020 Arm A.

**Table 36.** Subject Incidence of Treatment-Emergent Abnormal Chemistry Laboratory Tests per CTCAE 5.0 Toxicity Grade (Data cutoff: August 2023)

| | | Arm A Pirtobrutinib (N=116) Worst post-baseline grade n(%) | | | | |
|---|---|---|---|---|---|---|
| Lab Parameter | n | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Sodium Increased | 114 | 17 (14.9) | 17 (14.9) | 0 | 0 | 0 |
| Sodium Decreased | 114 | 18 (15.8) | 17 (14.9) | 1 ( 0.9) | 0 | 0 |
| Potassium Increased | 114 | 16 (14.0) | 9 ( 7.9) | 5 ( 4.4) | 1 ( 0.9) | 1 ( 0.9) |
| Potassium Decreased | 114 | 12 (10.5) | 11 ( 9.6) | 0 | 1 ( 0.9) | 0 |
| Glucose Decreased | 114 | 9 ( 7.9) | 6 ( 5.3) | 3 ( 2.6) | 0 | 0 |
| Creatinine Increased | 114 | 21 (18.4) | 17 (14.9) | 4 ( 3.5) | 0 | 0 |
| Lactate Dehydrogenase Increased | 114 | 8 ( 7.0) | 8 ( 7.0) | 0 | 0 | 0 |
| Calcium Increased | 113 | 14 (12.4) | 13 (11.5) | 1 ( 0.9) | 0 | 0 |
| Calcium Decreased | 113 | 20 (17.7) | 15 (13.3) | 5 ( 4.4) | 0 | 0 |
| Magnesium Increased | 110 | 10 ( 9.1) | 8 ( 7.3) | 0 | 2 ( 1.8) | 0 |
| Magnesium Decreased | 110 | 5 ( 4.5) | 5 ( 4.5) | 0 | 0 | 0 |
| Albumin Decreased | 112 | 11 ( 9.8) | 7 ( 6.3) | 4 ( 3.6) | 0 | 0 |
| Alkaline Phosphatase Increased | 92 | 9 ( 9.8) | 8 ( 8.7) | 1 ( 1.1) | 0 | 0 |
| Alanine Aminotransferase Increased | 114 | 22 (19.3) | 18 (15.8) | 4 ( 3.5) | 0 | 0 |
| Aspartate Aminotransferase Increased | 113 | 12 (10.6) | 11 ( 9.7) | 1 ( 0.9) | 0 | 0 |
| Bilirubin Increased | 114 | 18 (15.8) | 11 ( 9.6) | 6 ( 5.3) | 1 ( 0.9) | 0 |
| | | Arm B IdelaR (N=77) | | | | |
| Sodium Increased | 75 | 7 ( 9.3) | 7 ( 9.3) | 0 | 0 | 0 |
| Sodium Decreased | 75 | 16 (21.3) | 13 (17.3) | 2 ( 2.7) | 1 ( 1.3) | 0 |
| Potassium Increased | 75 | 14 (18.7) | 7 ( 9.3) | 6 ( 8.0) | 1 ( 1.3) | 0 |
| Potassium Decreased | 75 | 10 (13.3) | 8 (10.7) | 0 | 1 ( 1.3) | 1 ( 1.3) |
| Glucose Decreased | 75 | 2 ( 2.7) | 2 ( 2.7) | 0 | 0 | 0 |
| Creatinine Increased | 75 | 17 (22.7) | 13 (17.3) | 4 ( 5.3) | 0 | 0 |
| Lactate Dehydrogenase Increased | 75 | 22 (29.3) | 22 (29.3) | 0 | 0 | 0 |
| Calcium Increased | 75 | 15 (20.0) | 11 (14.7) | 2 ( 2.7) | 1 ( 1.3) | 1 ( 1.3) |
| Calcium Decreased | 75 | 20 (26.7) | 16 (21.3) | 4 ( 5.3) | 0 | 0 |
| Magnesium Increased | 74 | 11 (14.9) | 10 (13.5) | 0 | 1 ( 1.4) | 0 |
| Magnesium Decreased | 74 | 6 ( 8.1) | 4 ( 5.4) | 2 ( 2.7) | 0 | 0 |
| Albumin Decreased | 74 | 6 ( 8.1) | 2 ( 2.7) | 4 ( 5.4) | 0 | 0 |
| Alkaline Phosphatase Increased | 66 | 12 (18.2) | 11 (16.7) | 1 ( 1.5) | 0 | 0 |
| Alanine Aminotransferase Increased | 75 | 43 (57.3) | 22 (29.3) | 8 (10.7) | 11 (14.7) | 2 ( 2.7) |
| Aspartate Aminotransferase Increased | 75 | 34 (45.3) | 26 (34.7) | 6 ( 8.0) | 1 ( 1.3) | 1 ( 1.3) |
| Bilirubin Increased | 75 | 15 (20.0) | 10 (13.3) | 5 ( 6.7) | 0 | 0 |
| | | Arm B BendaR (N=32) Worst post-baseline grade n(%) | | | | |
| Lab Parameter | n | Any Grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Sodium Increased | 30 | 2 ( 6.7) | 2 ( 6.7) | 0 | 0 | 0 |
| Sodium Decreased | 30 | 3 (10.0) | 3 (10.0) | 0 | 0 | 0 |
| Potassium Increased | 29 | 0 | 0 | 0 | 0 | 0 |
| Potassium Decreased | 29 | 2 ( 6.9) | 2 ( 6.9) | 0 | 0 | 0 |
| Glucose Decreased | 30 | 0 | 0 | 0 | 0 | 0 |
| Creatinine Increased | 30 | 2 ( 6.7) | 2 ( 6.7) | 0 | 0 | 0 |
| Lactate Dehydrogenase Increased | 29 | 6 (20.7) | 6 (20.7) | 0 | 0 | 0 |
| Calcium Increased | 30 | 3 (10.0) | 2 ( 6.7) | 0 | 0 | 1 ( 3.3) |
| Calcium Decreased | 30 | 8 (26.7) | 7 (23.3) | 1 ( 3.3) | 0 | 0 |
| Magnesium Increased | 29 | 1 ( 3.4) | 1 ( 3.4) | 0 | 0 | 0 |
| Magnesium Decreased | 29 | 0 | 0 | 0 | 0 | 0 |
| Albumin Decreased | 29 | 2 ( 6.9) | 1 ( 3.4) | 1 ( 3.4) | 0 | 0 |
| Alkaline Phosphatase Increased | 26 | 4 (15.4) | 3 (11.5) | 1 ( 3.8) | 0 | 0 |
| Alanine Aminotransferase Increased | 29 | 3 (10.3) | 3 (10.3) | 0 | 0 | 0 |
| Aspartate Aminotransferase Increased | 29 | 2 ( 6.9) | 2 ( 6.9) | 0 | 0 | 0 |
| Bilirubin Increased | 29 | 5 (17.2) | 4 (13.8) | 0 | 1 ( 3.4) | 0 |

### *Vital Signs, Physical Findings, and Other Observations Related to Safety*

Analysis of vital signs in Study 20020 did not reveal any new safety concerns relative to overall assessment of AEs. No notable changes were observed between the medians of baseline and post-baseline values for diastolic and systolic blood pressure, heart rate, respiration rate, body weight, and temperature.

There was no clinically meaningful difference in vital sign or physical findings between Study 20020 Arm A and Arm B, or between Study 20020 Arm A and Study 18001 OMTSAS-200.

### *Discontinuation due to adverse events*

***Study 20020***

In pirtobrutinib-treated patients (Arm A), 20 (17.2%) patients experienced a TEAE that led to permanent treatment discontinuation in the updated safety data (August 2024 data cut); 6 (5.2%) patients had an event that was considered treatment-related.

In Arm B, 38 (34.9%) patients experienced a TEAE that led to permanent treatment discontinuation; 23 (21.1%) patients had an event that was considered treatment-related. Most of the permanent treatment discontinuations due to TEAEs in Arm B occurred on IdelaR (35 [45.5%] patients; 22 [28.6%] patients treatment-related). The System Organ Class with the most TEAEs leading to permanent treatment discontinuation in both arms was Infections and Infestations (Arm A: 9.5%; Arm B: 9.2%)

***Study 18001***

AE Leading to Drug Interruption

In the Study 18001 OMTSAS-200, 63 (11%) patients had AEs leading a that led to treatment discontinuation; 18 (3.1%) patients had an event that was considered treatment-related.

In the Study 18001 CSAS-200, 25 (11.8%) patients had AEs leading a that led to treatment discontinuation; 8 (3.8%) patients had an event that was considered treatment-related.

### *Post marketing experience*

No safety signals arising from post-marketing data have been identified as of 27 October 2023 Periodic Adverse Drug Experience Report date.

## 2.5.1. Discussion on clinical safety

*Introduction*

The clinical safety analysis is based on the results of the pivotal phase 3 study 20020, a global, randomized, open-label study comparing the efficacy and safety of pirtobrutinib 200 mg once daily (QD) as continuous monotherapy (Arm A) to Investigator's choice of either IdelaR or BendaR (Arm B) in CLL patients previously treated with a BTK inhibitor.

In addition, ongoing study 18001 (interim analysis of a phase 1 / 2 trial) provided supportive data from 588 patients who received at least 1 dose of pirtobrutinib as monotherapy at a starting dose of 200 mg QD without subsequent dose escalation irrespective of B-cell malignancy (OMTSAS-200). Among these subjects, there was a subgroup of 220 patients with CLL (CSAS-200).

*Exposure, demographics and baseline characteristics*

In Study 20020, as of the data cut-off date of 29 August 2024, 116 participants were included in the safety population Arm A (i.e. treated with at least 1 dose of pirtobrutinib as continuous monotherapy). The average daily pirtobrutinib dose was 189.6 mg/day in Arm A which is not far from the claimed posology.

The median duration of therapy for patients who received pirtobrutinib in Arm A was 15.05 months (range: 0.10, 33.41 months). The person-year at risk for safety evaluation was 146.6 PY in Arm A (PY

= the sum of the years for the TEAE observation periods across all patients). Most patients received between 1 and 24 cycles of pirtobrutinib. In the comparator Arm B, 109 patients were included and received or idelalisib + rituximab (IdelaR, n=77) or bendamustine + rituximab (BendaR, n=32). The median duration of therapy was shorter in the comparator group (7.08 months (range: 0.30, 29.01) for idelalisib and 4.73 months (range: 0.92, 12.19 months) for bendamustine) and 69.7 PY.

Given the difference in exposure in the two arms of the pivotal study, the MAH provided an overview of TEAE PT expressed in rate per patient year. Incidence rates were generally lower in Arm A compared with Arm B except for pneumonia and anaemia Both events are known ADRs for pirtobrutinib and are expected based on known mechanism of action of BTK inhibitors on B-cells and other immune cells. However, the incidence rates of Grade 3/4 pneumonia were similar in both arms and the incidence of Grade 3/4 anaemia was slightly lower in Arm A versus Arm B.

In study 18001, with the data cutoff of 26 January 2024 the median time on pirtobrutinib treatment was 10.15 and 20.63 months for OMTSAS-200 and CSAS-200 respectively.

From a safety point of view, no significant imbalance of demographic characteristics (sex ratio [70% of male patients in both arms], race, ethnicity, age, height and weight) were seen across Arm A and Arm B. However, it should be noted that the Asian population was more represented in the BendaR subgroup (n=14, 37.8%) compared to pirtobrutinib arm (n=14, 11.8%).

Likewise, baseline disease characteristics were overall well balanced. It is however noted that patients treated with pirtobrutinib were more likely to have stage IV Rai than those in the comparator arm (36.1% vs 26.9%). But conversely, there were more patients with stage III Rai in the comparator arm (17.6%) than in the pirtobrutinib-treated arm (6.7%). Thus, this is not expected to have a significant impact on the assessment of the safety profile.

Overall, there were no meaningful differences in prior cancer therapy between patients in Study 20020 Arm A and Study 20020 Arm B, with ibrutinib as the most frequently BTKi treatment administered (84.0% in Arm A and 89.1% in Arm B) and a mean of 3 lines of prior systemic therapy. Venetoclax was specified as a stratification factor in this study. With regard to concomitant medications, it was noted that patients in arm A were more frequently treated with cardiovascular medications vs in arm B. This could be weighed against the higher frequency of grade 3/4 TEAEs in the Cardiac Disorders SOC in arm A (n=4, 3.4%) compared to arm B (n=0) for an equivalent proportion of TEAE (6.0% vs 8.3%).

*Adverse events and treatment related AE*

In the pivotal study 20020, 108 pirtobrutinib treated patients (93.1%) experienced at least one AE (arm A) vs 107 patients (98.2%) in the comparator group (Arm B). According to the investigator, treatment-related AEs occurred in 71 (61.2%) patients in Arm A vs 90 patients (82.6%) in Arm B. Frequency of Grade 3 or 4 AEs and serious AE were numerically lower or similar in pirtobrutinib treated patients *vs* in the comparator group (respectively 55 (47.4%) and 55 (47.4%) patients *vs* 70 (64.2%) and 51 (46.8%)) patients in the comparator group. Discontinuations due to AEs or SAE were lower in Arm A compared to Arm B. As a whole, the rate of AEs was higher in arm B than in the arm A, as well as frequency of Treatment-related AEs, Grade 3 or 4 AEs and serious AE.

In study 20020 Arm A, the most common TEAE were pneumonia (n=26, 22.4%), anaemia (n=23, 19.8%), neutropenia (n=21, 18.1%), Cough (n=19, 16.4%), Diarrhoea (n=19, 16.4%), COVID-19 (n=15, 12.9%), Pyrexia (n=15, 12.9%)and Oedema peripheral (n=13, 11.2% each). In Arm B, the most common TEAE were Diarrhoea (n=34, 31.2%), pyrexia (n=29, 26.6%), nausea and fatigue (n=22, 20.2%); Covid-19 (n=20, 18.3%), anaemia, cough and vomiting (n=19, 17.4%), neutropenia (n=17, 15.6%) and headache (n=16, 14.7%).

Regarding pirtobrutinib-related AEs, 71 patients (61.2%) experienced at least 1 TEAE considered by the investigator to be related to pirtobrutinib including 33 (28.4%) patients with a Grade 3 or 4 and 16 (13.8%) patients with SAE. The treatment-related TEAEs most commonly reported in the initial submission were neutropenia (11.2%), anaemia (7.8%), diarrhoea (6.9%), fatigue, headache and neutrophil count decreased (5.2%) and pneumonia and thrombocytopenia (4.3%). This is consistent with the known safety profile of pirtobrutinib already authorised in MCL. In Arm B, 90 patients (82.6%) experienced at least 1 TEAE considered by the investigator to be related to IdelaR or BendaR including 49 (45.0%) patients with a Grade 3 or 4 and 23 (21.1%) patients with SAE. The treatment-related TEAEs most commonly reported in the initial submission were diarrhoea (14.7%), neutrophil count decreased and nausea (11.9%), AST increased (9.2%) and neutropenia and anaemia (7.3%). Increases in AST and ALT were more frequently reported in the comparator group (more than 10%) rather to pirtobrutinib group (less than 5%) which could be expected from the safety profile of idelalisib and bendamustine.

In study 20020, 20 (17.2%) patients discontinued pirtobrutinib due to the occurrence of at least 1 TEAE including 8 (6.9%) patients due to Grade 3 or 4 TEAE. TEAE in the initial submission were mainly from the SOCs Infections and infestations (n=6, 5.2%), Cardiac disorders (n=2, 1.7%) and Respiratory, thoracic and mediastinal disorders (n=2, 1.7%). In Arm B, 38 (34.9%) patients discontinued IdelaR or BendaR due to an AE including 22 (20.2%) patients with Grade 3 or 4. PT the most frequently reported in the initial submission were ALT increased, diarrhea, COVID-19, hypercalcemia, pneumonia, and rash. TEAE were considered related by the investigator in 14 patients (12.8%) mainly belonging to SOC Skin and subcutaneous tissue disorders (n=4) and Investigations (n=3).

The incidence of peripheral oedema was higher in the pirtobrutinib arm (n=13, 11.2%;) compared to Arm B (n=7, 6.4%). The difference was maintained in the exposure-adjusted analysis (15.5 vs. 10.8 patients with events per 100 patient-years). All events were of low grade (1 or 2) severity and one event led to dose reduction. In the integrated safety population, at the time of the initial submission, peripheral oedema (any grade) was reported in 77 (10.9%) patients. The majority of events were Grade 1 and/or 2. Two (0.3%) patients reported Grade 3 peripheral oedema. Of note, peripheral oedema is listed as an ADR for other approved BTK inhibitor agents. Based on the review of integrated safety data from Study 18001 and Study 20020, peripheral oedema is now included as an ADR for pirtobrutinib in the SmPC. Of the 77 patients with peripheral oedema, only 5 cases had concurrent CVS events and for only one of them the CVS event was associated with cardiac decompensation; the evidence of a causal association of peripheral oedema with underlying CVS disease in these cases is inconclusive. None of these cardiovascular adverse events reported within one month of onset of peripheral enema were considered related to pirtobrutinib. At this moment, there is no evidence of a causal association between pirtobrutinib and peripheral oedema as a consequence of a cardiovascular event. Therefore, no further updates to the SmPC are warranted with respect to peripheral oedema in relation to CVS causes.

Dose reduction was more frequent in the comparator arm (n=40, 36.7%) compared to the pirtobrutinib arm (n=13, 11.2%). However, dose interruption occurred more frequently in the pirtobrutinib group (n=79, 68.1%) than in the comparator group (n=57, 52.3%).

Data from Study 18001 OMTSAS-200 regarding discontinuation, dose reduction or drug interruption were overall consistent with those described in the pivotal study 20020.

*Fatal cases and AESI*

In study 20020, no patients died from an adverse event whilst on treatment. In Arm A 9 (7.8%) died due to AEs within 30 days of the last study drug dose and 6 (5.2%) after 30 days of last dose. None of the deaths in Arm A patients were considered related to pirtobrutinib by the investigator. In Arm B, 9

patients (8.3%) died due to AEs within 30 days of the last study drug dose (IdelaR: 7 [9.1%] patients; BendaR: 2 [6.3%] patients).

The most commonly reported fatal AES were COVID-19 pneumonia in Arm A (3 patients, 2.6%) and pneumonia in Arm B (2 patients, 1.8%). A known risk of pirtobrutinib is pneumonia (frequency category common), and this PT is one of the most reported TEAE (15.5%).

In Study 18001, 25 subjects (11.4%) had a serious TEAE with fatal outcome in CSAS-200 and 44 subjects (7.5%) in OMTSAS-200. The most frequent TEAEs associated with fatal outcome were COVID-19 pneumonia (respectively 4 [1.8%] and 8 [1.4%]), COVID-19 (5 [2.3%] and 5 [0.9%]), respiratory failure (2 [0.9%] and 5 [0.9%]) and septic shock (2 [0.9%] and 3 [0.5%]).

In study 20020 Arm A, SAEs were reported in 55 (47.4%) patients in Arm A, mainly pneumonia (18 [15.5%] patients), COVID-19 pneumonia (4 [3.4%] patients), anaemia (3 [2.6%] patients) COVID-19 and pyrexia (2 [1.7%] patients each). Pneumonia was the most commonly reported SAE, most frequently in Arm A as describe above. In Arm B, SAEs were reported in 51 (46.8%) patients, mainly pneumonia (12 [11%] patients), COVID-19 (5 [4.6%] patients), febrile neutropenia and diarrhoea (4 [3.7%] patients each), COVID-19 pneumonia, Infusion related reaction and pyrexia (3 [2.8%] patients).

The MAH has described the following AESI: infections, bleeding (including bruising, petechiae and purpura, and haemorrhage), cytopenias (including neutropenia, anaemia, and thrombocytopenia) and atrial fibrillation and flutter. Overall, these AESI are already known and described in the SmPC, including the mechanistic plausibility. The data from study 18001 do not provide new information on these AESIs.

Overall, the incidence of any grade infections was higher in Arm A (63.8%) than in Arm B (49.5%), and the incidence of infections grade 3 or higher was higher in Arm A (29.3%) compared to Arm B (23.9%). However, the exposure-adjusted incidence rate of any grade infection was lower in Arm A (94.5 per 100 PY) than in Arm B (125.5 per 100 PY).

Bleeding events (bleeding, bruising, petechiae & purpura and haemorrhage) were more frequent in arm A than in arm B (mainly grade 1 or 2), including for serious events and serious pirtobrutinib related TEAEs. No fatal case occurred in Arm A. Bleeding has only led to discontinuation of pirtobrutinib in rare cases.

Cytopenias (anaemia, neutropenia and thrombocytopenia) were less frequent in arm A than in arm B (with the exception of anaemia, for which the related cases occurred at the same frequency). Cytopenias were more frequently grade 3 or 4 but infrequently serious. No fatal case occurred in Arm A. Only in rare cases did bleeding lead to discontinuation of pirtobrutinib.

Three cases of atrial fibrillation occurred in Arm A including one non-serious but related case, but this risk is already adequately reflected in the product information.

*Laboratory findings*

Overall, laboratory findings are consistent with the known safety profile of pirtobrutinib, including cytopenia and blood chemistry. Analysis of laboratory data did not reveal any information that would provide new insight into the known safety profile of pirtobrutinib.

*Safety in special population*

Regarding safety in special population, no subgroups analysis for the pivotal study analysis were provided. During the initial marketing authorisation assessment, no differences were suggested for intrinsic factors related to gender or race, and it was difficult to draw conclusions about safety in a

special population due to the lack of a control arm in the 18001 study. Safety in special population had been described by age groups (<65 y; 65-75 y; 75-84 y; ≥85 y) and the small number of patients over 85 years of age precluded drawing conclusions about the safety profile of elderly patients. No new information on these special populations is expected as part of this extension of indication.

### 2.5.2. Conclusions on clinical safety

Overall, the safety profile of pirtobrutinib in patients treated for CLL is in line with the known safety profile for the already authorised indication in relapsed or refractory MCL. It is mainly characterised by infectious disorders (especially pneumonias) and Blood and lymphatic system disorders (neutropenia and anaemia) which are reflected in the product information. The only new ADR identified from the new safety information is "oedema peripheral", which has been included in the SmPC section 4.8 with a frequency of very common. Other changes such as revisions in frequencies and clarifications have also been implemented in 4.8 of the SmPC.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.1 with the following content:

### *Safety concerns*

| **Summary of Safety Concerns** | |
|---|---|
| Important Identified Risks | Serious haemorrhages<br>Serious infections<br>Atrial fibrillation and atrial flutter |
| Important Potential Risks | Second primary malignancies other than non-melanoma skin cancer<br>Second primary non-melanoma skin cancer |
| Missing Information | None |

## *Pharmacovigilance plan*

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| **LOXO-BTK-18001**<br>A Phase 1/2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)<br>**Status:**<br>ongoing | To integrate the analysis for second primary malignancies for a 5-year follow-up | - second primary malignancies other than non-melanoma skin cancer<br>- second primary non-melanoma skin cancer | An interim analysis is planned for submission to EMA by September 2025 | Final report by June 2028 |
| **LOXO-BTK-20019**<br>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>**Status:**<br>ongoing | | | | |
| **LOXO-BTK-20020**<br>A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)<br>**Status:**<br>ongoing | | | | |
| **LOXO-BTK-20023**<br>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 (BRUIN-CLL-313)<br>**Status:**<br>ongoing | | | | |
| **LOXO-BTK-20030**<br>A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Ibrutinib in High-Risk Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL 314)<br>**Status:**<br>ongoing | | | | |

## *Risk minimisation measures*

| Safety Concern | Risk Minimisation Measures |
|---|---|
| Serious haemorrhage | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4, and 4.8<br><br>• Recommendation to monitor patients for signs and symptoms of bleeding is included in SmPC Section 4.4.<br>• Recommendation to consider the benefit-risk of anticoagulant or antiplatelet therapy when co-administered with pirtobrutinib is included in SmPC Section 4.4. A statement is included in the same section that the use of pirtobrutinib has not been studied with warfarin or other vitamin K antagonists.<br>• Recommendation to consider the benefit-risk of withholding pirtobrutinib for 3 to 5 days pre- and post-surgery depending on the type of surgery and risk of bleeding is included in SmPC Section 4.4.<br>• Guidance on dose interruption based on the grade of the bleeding event and whether it occurs with thrombocytopenia is provided in SmPC Section 4.2.<br>Additional risk minimisation measures: Not applicable |
| Serious infections | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4, and 4.8<br><br>• Recommendation to consider prophylaxis in patients who are at increased risk for opportunistic infections is included in SmPC Section 4.4.<br>• Guidance on dose interruption based on the grade of infection and whether it occurs with neutropenia is included in SmPC Section 4.2.<br>Additional risk minimisation measures: Not applicable |
| Atrial fibrillation and Atrial flutter | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4, and 4.8<br><br>• Recommendation to monitor for signs and symptoms of atrial fibrillation and atrial flutter and obtain an ECG as medically indicated is included in SmPC Section 4.4.<br>• Guidance on dose interruption based on the grade of atrial fibrillation/atrial flutter is included in SmPC Section 4.2.<br><br>Additional risk minimisation measures: Not applicable |
| Second primary malignancies other than non-melanoma skin cancer | Routine risk minimisation measures:<br>SmPC Sections 4.2 4.4,<br><br>• Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4.<br>Additional risk minimisation measures: Not applicable |

| Safety Concern | Risk Minimisation Measures |
|---|---|
| Second primary non-melanoma skin cancer | Routine risk minimisation measures:<br>SmPC Sections 4.2 and 4.4,<br><br>• Recommendation to monitor patients for the appearance of skin cancers and advise protection from sun exposure is included in SmPC Section 4.4.<br>Additional risk minimisation measures: Not applicable |

Abbreviations: ECG = electrocardiogram; SmPC = summary of product characteristics; SPM: second primary malignancy.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- the structure and design of the revised package leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The claimed indication for this extension application is the following: "*Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor.*"

### 3.1.2. Available therapies and unmet medical need

The presentation and clinical course of CLL are highly variable, ranging from asymptomatic, indolent disease that may never require therapy (in approximately 30% of patients) to active disease. Numerous therapeutic options are now available for the treatment of relapsed or refractory CLL, including other oral BTK inhibitors such as acalabrutinib (Calquence) or zanubritinib (Brukinsa) that are associated by improvement of QoL with easier treatment administration.

Despite these major advances, CLL remains incurable.

### 3.1.3. Main clinical studies

The main evidence for efficacy and safety is based on study 20020, a phase 3, randomized, multicenter, and open-label controlled study in patients with relapsed or refractory CLL previously treated with a BTK inhibitor. Supportive data from Phase 1/2 Study 18001 in the same disease setting were also provided.

Patients enrolled in Study 20020 received either (ratio 1:1) receive pirtobrutinib (Arm A) or Investigator's choice (Arm B): bendamustine + rituximab (BendaR) or idelalisib and rituximab (IdelaR). Presence of a 17p deletion and previous venetoclax use were chosen as stratification factors, which is considered relevant since both are relevant prognosis factors. Pirtobrutinib was administered orally at 200 mg once daily and was continued until disease progression or unacceptable toxicity.

PFS was chosen as the primary efficacy endpoint and OS was the key secondary endpoint.

## *3.2. Favourable effects*

Pirtobrutinib monotherapy showed a clinically meaningful increment in IRC-assessed PFS compared to Arm B (HR=0.536; 95% CI: 0.385, 0.746). The median PFS by IRC assessment for Arm A was 13.96 months (95% CI: 11.24, 16.56) and for Arm B was 8.74 months (95% CI: 8.08, 10.38). The median follow-up time for Arm A was 19.35 months (95% CI: 16.66, 22.14) and for Arm B was 17.74 months (95% CI: 13.93, 22.90).

Median PFS by Investigator assessment for Arm A was 15.28 months (95% CI: 12.81, 19.94) and 9.20 months (95% CI: 7.33, 10.64) for Arm B. The median follow-up time was 19.38 months (95% CI: 16.72, 21.98) in Arm A and 17.54 months (95%CI: 13.93, 22.90) in Arm B. Concordance between IRC and INV-assessed PD was high for both arms, with a PD concordance rate of 81.5% (95% CI: 73.4, 88.0) in Arm A and 89.9% (95% CI: 83.0, 94.7) in Arm B.

Median TTNT was 23.95 months (95% CI: 17.84, 29.67) versus 10.91 months (95% CI: 8.74, 12.48) in Arm B.

Data from crossover patients by were overall consistent with those results, further supporting the relevance of pirtobrutinib treatment in the claimed indication.

Sensitivity analyses of PFS based on IRC assessments were performed and support the slight improvement in PFS associated with pirtobrutinib monotherapy compared to Arm B (IdelaR or BendaR). A trend in favour of pirtobrutinib treatment was also observed in PFS subgroup analyses.

## *3.3. Uncertainties and limitations about favourable effects*

In pivotal Study 20020, patients initially allocated to IdelaR or BendaR could crossover to pirtobrutinib, upon confirmation of disease progression by IRC. This crossover approach hampers the interpretation of efficacy data in the control arm. Median OS (95% CI) was reported as 29.67 (27.10, NE) and NR (28.88, NE) in the pirtobrutinib and control arms respectively which does not indicate a detrimental effect for pirtobrutinib treatment. However, survival data were missing or unknown in 12 patients in Arm A and 22 patients in Arm B, and the CHMP recommended that the final OS data be submitted when available.

## 3.4. Unfavourable effects

The safety profile of pirtobrutinib in patients treated for CLL is overall consistent with the known safety profile previously described for the already authorised indication in relapsed or refractory MCL.

In Study 20020 Arm A (N=116), the most common TEAE were pneumonia (n=26, 22.4%), anaemia (n=23, 19.8%), neutropenia (n=21, 18.1%), Cough (n=19, 16.4%), Diarrhoea (n=19, 16.4%), COVID-19 (n=15, 12.9%), Pyrexia (n=15, 12.9%); and Fatigue, Headache, Nause and Oedema peripheral (n=13, 11.2% each). Regarding pirtobrutinib-related AEs, 71 patients (61.2%) experienced at least 1 TEAE considered by the investigator to be related to pirtobrutinib including 33 (28.4%) patients with a Grade 3 or 4 and 16 (13.8%) patients with SAE. The treatment-related TEAEs most commonly in the initial data cutoff reported were neutropenia (11.2%), anaemia (7.8%), diarrhoea (6.9%), fatigue, headache and neutrophil count decreased (5.2%) and pneumonia and thrombocytopenia (4.3%).

Discontinuations due to AEs or SAE were lower in Arm A compared to Arm B. As a whole, the rate of AEs was higher in arm B than in the arm A, as well as frequency of Treatment-related AEs, Grade 3 or 4 AEs.

The following AESI (composite terms) were described by the MAH: infections (n=74, 63.8%), bleeding (n=25, 21.6%) cytopenias [neutropenia (n=31, 26.7%); anaemia (n=24, 20.7%) and thrombocytopenia (n=11, 9.5%)] and atrial fibrillation and flutter (n=3, 2.6%). These AESI are already known and described in the SmPC, including the mechanistic plausibility.

Overall, no new safety signal emerges from the review of the data provided when compared to those known as part of the established safety profile of pirtobrutinib.

## 3.5. Uncertainties and limitations about unfavourable effects

Patients were exposed slightly longer to pirtobrutinib than the comparator: the median duration of therapy for patients who received pirtobrutinib was higher in Arm A (15.05 months) compared to Arm B (7.08 months for IdelaB and 4.73 months for BendaB) which was still considered insufficient to properly characterize the safety profile of pirtobrutinib in the claimed indication. Nevertheless, additional characterisation of the risks associated with pirtobrutinib is expected from the ongoing studies which are already included in the product's RMP.

## 3.6. Effects Table

**Table 37**. Effects Table for pirtobrutinib for the treatment of adult Patients with Chronic Lymphocytic Leukaemia who have been previously treated with a Bruton's tyrosine kinase inhibitor data cut-off (29 August 2024).

| Effect | Short description | Unit | Jaypirca | IdelaR or BendaR | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| PFS | Median time from randomisa-tion until the occurrence of PD | Months | 13.96 (11.24,16.56) | 8.74 (8.08,10.38) | The treatment effect for PFS was robust and | Study 20020, ITT Population |

| Effect | Short description | Unit | Jaypirca | IdelaR or BendaR | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| | by IRC, per iwCLL 2018 criteria, or death from any cause in the absence of PD. | | HR = 0.536 (0.385, 0.746) | | consistent in subgroup analyses and supported by secondary endpoints in the trial | |
| **Unfavourable Effects** | | | | | | |
| Pneumonia | Incidence | % | 22.4 | 11.9 | Data consistent with known safety profile from MCL and the larger pooled safety data (Study 18001 OMTSAS-200) | Study 20020, Safety Population |
| Bleeding | Incidence | % | 21.6 | 10.1 | | |
| Anaemia | Incidence | % | 19.8 | 17.4 | | |
| Neutropenia | Incidence | % | 18.1 | 15.6 | | |
| Atrial fibrillation | Incidence | % | 2.6 | 0.9 | | |

*Abbreviations: BendaR = bendamustine + rituximab; HR = hazard ratio; IdelaR = idelalisib + rituximab; IGHV = immunoglobulin heavy chain variable region gene; INV = investigator; IRC = independent review committee, ITT = intention to treat; iwCLL = International Workshop on Chronic Lymphocytic Leukaemia; MCL= Mantle Cell Lymphoma; OMTSAS = overall monotherapy safety population receiving pirtobrutinib at 200 mg dose without subsequent dose escalation; PD = disease progression; PFS = progression-free survival.*

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The pivotal study for this extension application is well-designed, with a patient sample representative of the target population: adult patients with relapsed or refractory CLL previously treated by a BTK inhibitor at low, intermediate or high risk of progression or death. The choice of IdelaR or BendaR as comparators is appropriate given the treatment options available at study initiation.

The proposed dosing regimen was consistent with results from the Phase I/II study 18001 and in line with the approved dosage in MCL. Adequate risk minimization measures were implemented to ensure patient safety. Overall, the study integrity was preserved, with the major protocol deviations having only a limited impact.

The reported 5.2-month improvement in PFS for patients treated with pirtobrutinib compared to the control treated patients is considered clinically relevant. Despite the allowance of crossover and missing survival data, no detrimental effect on OS has been observed to date in the pirtobrutinib treated arm.

Overall, the safety profile of pirtobrutinib in patients treated for CLL seems consistent with the known safety profile already described for pirtobrutinib in relapse or refractory setting, MCL.

47.4% of the patients had at least 1 Grade 3/4 TEAE, and serious TEAEs occurred in 47.4% of participants. The most common TEAE were anaemia, neutropenia and pneumonia. All these risks are already known for pirtobrutinib and are considered manageable with the existing warnings in the product information.

### 3.7.2. Balance of benefits and risks

Pirtobrutinib has demonstrated to confer clinically relevant benefit in the treatment of adult patients with chronic lymphocytic leukaemia who have been previously treated with a Bruton's tyrosine kinase. This is considered to outweigh its toxicity which is in line with the known safety profile of pirtobrutinib and which can be managed adequately with the routine and additional risk minimisation measures that are already in place for this product.

## *3.8. Conclusions*

The overall B/R of Jaypirca is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor for JAYPIRCA, based on interim results from study LOXO-BTK-20020 (BRUIN CLL-321); this is a phase 3 open-label, randomized study of LOXO-305 versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in BTK inhibitor pretreated CLL/SLL.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.1 of the RMP has also been submitted.

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, only amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

## *Similarity with authorised orphan medicinal products*

The CHMP by consensus is of the opinion that Jaypirca is not similar to Gazyvaro within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.