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Pirtobrutinib *versus* venetoclax in covalent Bruton tyrosine kinase inhibitor-pretreated chronic lymphocytic leukemia: a matching-adjusted indirect comparison

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Running head: MAIC of pirtobrutnib vs venetoclax post-cBTKi

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Authorship Contributions (CRediT Statement)

Othman Al-Sawaf: Conceptualization; Writing – review and editing

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Data sharing statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Key Points

- In a MAIC, pirtobrutinib had comparable PFS and OS to continuous venetoclax monotherapy in patients with cBTKi-pretreated CLL.
- Pirtobrutinib was associated with improved ORR and favorable overall safety profile compared to venetoclax in cBTKi-pretreated CLL.

Abstract

Venetoclax is a standard treatment for patients with CLL following covalent BTK inhibitor (cBTKi) therapy, despite relatively limited prospective data in this setting. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that was designed to overcome the pharmacologic limitations of cBTKi and re-establish BTK inhibition. An unanchored matching-adjusted indirect comparison (MAIC) was conducted to estimate the treatment effect of pirtobrutinib versus venetoclax monotherapy in patients with cBTKi pre-treated CLL. Data from patients with CLL who were venetoclax-naïve and pre-treated with cBTKi received pirtobrutinib (n=146) in the phase 1/2 BRUIN study were compared with the only identified trial of patients with CLL receiving venetoclax after a cBTKi (n=91), as administered as monotherapy until progression. Outcomes included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and treatment-emergent adverse events (TEAEs). Both unweighted and weighted analyses were conducted. PFS and OS of pirtobrutinib and venetoclax were comparable in both unweighted and weighted analyses (weighted hazard ratios for PFS: 1.01, 95% CI: 0.58-1.73, p=0.98 and OS: 0.64, 95% CI: 0.25-1.67, p=0.34). ORR was significantly higher for pirtobrutinib (80.2% vs 64.8%, p=0.01). Grade ≥3 TEAEs were lower in weighted analyses for pirtobrutinib vs venetoclax (all p<0.01), except for pneumonia, which was similar. These results suggest that pirtobrutinib may also be considered as an effective and well-tolerated treatment for patients with relapsed CLL following cBTKi.

Introduction

Covalent Bruton tyrosine kinase inhibitor (cBTKi) therapy has increasingly become a standard of care worldwide for patients with chronic lymphocytic leukemia (CLL). Despite the marked efficacy of these agents, the majority of patients will eventually either progress or otherwise become intolerant to these agents, and as a result, the majority of patients will ultimately require additional treatment to achieve long-term disease control.[1] Following progression or intolerance on cBTKi therapy, the BH3 mimetic agent and B-cell lymphoma-2 inhibitor (BCL2i) venetoclax, administered either alone or in combination with an anti-CD20 antibody, has become an important standard of care.[1-4] While several retrospective studies, as well as pooled analyses from early-phase clinical trials, have evaluated the effectiveness of venetoclax post-cBTKi,[5-8] no randomized trials of venetoclax have been conducted exclusively in the post-cBTKi setting. The only prospective trial data of venetoclax in this setting is from a subset analysis of 91 heavily pre-treated patients who had received at least one cBTKi. In the published interim analysis of these data with a median follow up of 14 months, in which venetoclax was administered as a monotherapy continuously until progression, intolerance or withdrawal, the objective response rate (ORR) was 65% and median progression-free survival (PFS) was 24.7 months.[9] As this is not feasible or desirable for all patients, alternative safe and effective treatment options for patients with CLL after failure of cBTKi therapy are warranted. While many specialists and institutions have gained experience in the safe administration of venetoclax, careful patient selection and attention to patient care remain critical with adherence to the recommended ramp-up phase of treatment to avoid the serious adverse event (AE) of tumor lysis syndrome (TLS), which often requires administration of uric acid lowering agents, and, less commonly, the need for hospitalization for TLS monitoring.[10] Therefore, a need remains for additional safe and effective treatment options for patients with CLL after failure of cBTKi therapy.

Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi, that inhibits both wildtype and C481-mutant BTK with equal low nM potency and minimal in vitro off-target kinase activity. Pirtobrutinib is currently under investigation in multiple phase 3 trials for patients with CLL (NCT05023980, NCT05254743, NCT04666038, and NCT04965493), and is approved for use in the US among patients with mantle cell lymphoma after at least two lines of therapy, including a cBTKi.[11, 12] Pirtobrutinib has been studied in the phase 1/2 BRUIN trial (NCT03740529) for patients with B-cell malignancies, including 279 patients with CLL/SLL who received prior cBTKi therapy.[13] In this cohort of patients who had a median of 3 prior lines of therapy (at least one containing a cBTKi), the ORR according to independent review (inclusive of partial response with lymphocytosis [PR-L]) was 73.3%, with a median PFS of 19.6 months. Among the 147 patients who had no prior BCL2i therapy, the median PFS was 22.1 months. Given these data, there are important questions regarding the comparative outcomes of single-agent pirtobrutinib and venetoclax in the post-cBTKi setting.

The primary objective of this study was to estimate the treatment effect for pirtobrutinib (BRUIN, NCT03740529) versus venetoclax continuous monotherapy among patients with CLL who previously received treatment with a cBTKi in an unanchored matching-adjusted indirect comparison (MAIC).

Methods

A systematic literature review was conducted to identify published clinical trials of single-agent venetoclax among patients with relapsed/refractory CLL in the post-cBTKi setting (Supplementary Tables 1 and 2). One study met eligibility criteria (NCT02141282).[9] As only summary data were available from this trial, no selection criteria were applied to the cohort of patients treated with venetoclax; all available data were used. The analysis dataset from BRUIN was limited to patients diagnosed with CLL who had prior cBTKi exposure and excluded

patients with prior BCL2i exposure, prior stem cell transplantation, or histopathological evidence of Richter transformation to more closely match the eligibility criteria for the venetoclax trial.[9]

The primary analysis used an informed covariate approach, which limited the covariates used in the reweighting exercise to those with literature supporting their prognostic value. Covariates in the primary analysis included median patient age, median number of prior therapies, percent of patients who discontinued the prior cBTKi due to progression, as well as percent of patients with del(17p), del(11q), or unmutated immunoglobulin heavy variable (IGHV) gene, respectively. The following outcomes were reported in both trials and included in the MAIC: ORR by investigator assessment; PFS; OS; TEAE; and proportion of patients who discontinued treatment due to an AE.

This comparison of pirtobrutinib versus venetoclax followed best practices in the identification of comparator studies and analysis of data using an unanchored MAIC.[14] MAIC methods overcome limitations of naïve cross-trial comparisons[14] by reducing ecological bias[15] and allow for a more robust comparison between interventions that are not directly compared in a randomized trial. MAIC requires that individual patient-level data are available from at least one study, but are not available from all studies to be investigated.[16]

The method described by Guyot et al.[17] was used to simulate patient-level data from Kaplan-Meier charts and associated risk tables for the venetoclax trial. A lack of agreement was noted between the number at risk and the number censored in the published figures for PFS and OS in the venetoclax trial.[9] As such, the digitized curve (generated using PlotDigitizer) was used to recalculate the number at risk to match the published image.

Patients in the pirtobrutinib cohort were re-weighted to match the measures of central tendency and proportion of patients for the characteristics reported for venetoclax. Since only summary baseline data were available from the venetoclax trial, the logistic regression model was estimated using the method of moments so that the weight for each individual patient was equal to the patient's estimated odds (propensity) of being in the BRUIN study (pirtobrutinib) versus NCT02141282 (venetoclax).[14, 16, 18] Distribution of the weights applied were inspected for potential extreme values, which could be indicative of poor overlap between the study populations in the distributions of patient characteristics.[19]

Time-to-event outcomes were compared using Cox regression and log-rank tests; ORR and TEAEs were evaluated using Fisher's exact test. All outcomes were evaluated both as unweighted and weighted comparisons. Analyses were conducted using R4.1.2 (Posit Software PBC). Sensitivity analyses were conducted as summarized in the Supplementary Materials.

Results

Trials included in the analysis

The BRUIN trial began enrollment of patients to be treated with pirtobrutinib March 2019, and the study is ongoing. Data were available for analysis from the July 2022 data cut at the time of this analysis. The venetoclax trial enrolled patients between September 2014, and November 2016, and the study was ongoing at the time of the publication of this interim analysis of the subset of patients with prior cBTKi exposure. Given the differences in time periods, a summary of the prior therapies received by patients is presented in Supplementary Table 3. To the best of our knowledge, no additional updates of this subset of patients treated with venetoclax have been presented. Both studies enrolled patients with CLL who had relapsed or refractory disease. For this analysis, patients in both cohorts were limited to those with prior cBTKi

exposure and without prior venetoclax. After applying eligibility criteria, a total of 146 patients were available from the BRUIN trial for comparison to the venetoclax monotherapy cohort (n=91). Of note, there were no patients excluded due to having pathological evidence of Richter's transformation.

Primary analyses

The pirtobrutinib (n=146) and venetoclax (n=91) study cohorts included in this MAIC are presented in Table 1. Before matching, there were some differences between the trial populations studied, with patients in the pirtobrutinib study having a lower median number of prior lines of therapy, slightly older age, more patients who had discontinued the cBTKi due to progression, and a lower rate of unmutated IGHV. Median follow-up was 21.3 months and 14.0 months for the pirtobrutinib and venetoclax cohorts, respectively. After reweighting, all available characteristics were well balanced between cohorts, resulting in an effective sample size of 61.

There were no significant differences observed in the unweighted or weighted comparisons of pirtobrutinib versus venetoclax for either PFS or OS. Median PFS for pirtobrutinib was 22.1 months in unweighted and 19.4 months in weighted analyses, versus 24.7 months for venetoclax. Median OS for pirtobrutinib was not reached. The weighted HR for PFS was 1.01 (95% CI: 0.58-1.73, p=0.98) and for OS was 0.64 (95% CI: 0.25-1.67, p=0.34) (Figures 1 and 2, respectively). Of note, 6 of the 28 (21.4%) observed deaths included in these time-to-event outcomes in the pirtobrutinib cohort were COVID19-related.

Response outcomes according to iwCLL in both unweighted and weighted analyses of pirtobrutinib versus venetoclax are presented in Table 2. ORR was 80.2% for patients treated with pirtobrutinib (inclusive of PR-L) versus 64.8% for patients treated with venetoclax (weighted

OR= 2.22, 95% CI: 1.16-4.29, p = 0.01). The rates of complete responses (CR) were 1.4% and 8.8%, respectively.

Each grade ≥3 TEAE reported in Jones et al.[9] and recorded by both trials are summarized in Table 3. In both unweighted and weighted analyses, each grade ≥3 TEAE compared in this study was significantly lower for pirtobrutinib (all p<0.05), except for pneumonia, which was not significantly different between pirtobrutinib and venetoclax (weighted p=0.06). Similarly, each any grade TEAE demonstrated consistent findings for these differences between the two cohorts (Supplemental Table 5). There was no difference in the proportion of patients who discontinued therapy due to an AE in both unweighted and weighted analyses (weighted OR = 0.44, 95% CI: 0.09-1.92, p = 0.32). Each TEAE recorded in the supplemental venetoclax material that was also recorded in the pirtobrutinib trial is included in Supplementary Table 6, which reports details of events such as infection, gastrointestinal disorder, metabolism and nutrition disorders, and neoplasms.

Sensitivity analyses

There were no differences between pirtobrutinib and venetoclax in the primary analysis, which limited the reweighting factors to those with known prognostic value, and sensitivity analyses, which included all baseline covariates (Supplementary Table 4). There were no significant differences in PFS, OS or treatment discontinuation due to adverse events. Each grade ≥3 TEAE reported by both trials remained significantly lower for pirtobrutinib (all p<0.05), except for pneumonia, which was not also significantly different between pirtobrutinib and venetoclax (weighted p=0.06) in sensitivity analyses. There were extreme weights observed upon inspection as evidenced by the sharp drop in PFS, as a result of an event occurring for such a patient. Sensitivity analyses removing the patients with extreme weights did not change the statistical significance or direction of the HR or OR of any reported outcomes (data not shown).

Discussion

Venetoclax has become an important treatment option for patients with relapsed/refractory CLL following a cBTK inhibitor, although no randomized studies have been completed exclusively in this treatment setting. More recently, pirtobrutinib has shown promising activity in patients with relapsed/refractory CLL after cBTKi use and continues under investigation in this setting.[13] However, no direct head-to-head data have been described between single-agent pirtobrutinib and venetoclax among these patients. Therefore, in the absence of a comparative trial, this MAIC was conducted to investigate the potential comparative outcomes of pirtobrutinib versus venetoclax in the treatment of CLL in the post-cBTKi setting. To do so required focusing on venetoclax monotherapy administered continuously until progression, as no data were identified evaluating time-limited venetoclax in combination with an anti-CD20 antibody in this treatment setting and highlights the limited published data for venetoclax post-cBTKi. While real-world data show that venetoclax monotherapy is the most common BCL2i-based therapy used post-cBTKi,[20] other regimens, such as venetoclax plus rituximab or obinutuzumab, are also considered reasonable approaches in the relapsed/refractory setting. The landmark Murano trial, which studied a 24-month time limited duration of venetoclax in addition to rituximab, only included 5 patients (2.5% of all patients in this arm of the trial) who had received prior B-cell receptor inhibitor-based therapy.[21] There are no known trials of venetoclax plus obinutuzumab after cBTKi therapy, as this regimen was investigated in the first-line setting, limiting the ability to investigate other BCL2i-based therapies in the post-cBTKi setting.

The data from this MAIC suggest improved ORR associated with pirtobrutinib compared to venetoclax, with no differences observed in PFS and OS outcomes. ORR values reported in the venetoclax study were investigator-assessed; it is unknown if a comparison of response by independent review would have resulted in these same outcomes. Moreover, this analysis

demonstrated that the comparative AE profiles of these agents potentially favored pirtobrutinib. Specifically, anemia, neutropenia, febrile neutropenia, and thrombocytopenia were each significantly lower in patients treated with pirtobrutinib; however, pneumonia and treatment discontinuations due to an AE were not different between pirtobrutinib and venetoclax.

This MAIC raises important questions about the sequencing of agents, particularly regarding the value of exhausting BTK pathway inhibition versus switching therapy based on mechanism of action. Pending the readout of upcoming randomized trials of pirtobrutinib, the placement of this agent in the future care of patients with CLL remains an area of further evaluation. There is a need to not only rely on the results of these trials, but to proactively assess treatment sequencing of these agents in the real-world setting to optimize care for patients with CLL when a cBTKi is no longer an option. A multi-center cohort study evaluated outcomes of 63 patients with cBTKi pretreated CLL or Richter Transformation (RT) who received treatment after non-covalent BTKi therapy, with more than 90% of these patients having received pirtobrutinib.[22] In this cohort, 8 patients with CLL and 2 with RT received venetoclax after the non-covalent BTKi. PFS for venetoclax for those with CLL was 14 months, and response to venetoclax was observed in 7 of the 10 patients.[22] In a broader cohort of 247 patients enrolled the BRUIN trial with CLL who received prior cBTKi therapy, including 41% who had also received a BCL2i, the objective tumor response rate (ORR) was 73.3% and PFS was a median of 19.6 months.[13] Pirtobrutinib has furthermore demonstrated efficacy in patients after both a prior cBTKi and BCL2i, with an ORR of 70.0% and median PFS of 16.8 months.[13]

Although the data from this MAIC further support the BRUIN trial data regarding the comparable efficacy of pirtobrutinib to venetoclax after prior non-covalent BTKi therapy, the sample size is small and the analysis only includes two trials; additional data are needed to inform treatment decision-making regarding the sequencing of care of patients with CLL. While a MAIC is an

improved approach over the indirect side-by-side comparison of trials due to the reweighting algorithm, there are inherent limitations to indirect analyses that should be recognized when evaluating the findings from this study. It should be noted that in this MAIC, there were no patient-level data available for venetoclax. It is not possible to completely know if the outcomes observed would be replicated in a trial where cohorts were balanced at the individual patient level by means of randomization; while the mean/proportion of patients can be balanced, the distribution of outcomes is unknown. Prior research has shown that outcomes using MAIC methods may not always correspond to analyses where patient-level data are known for both treatment groups, but have also shown directional consistency in other studies and remain an area of uncertainty.[23-25] Additionally, the reweighting exercise resulted in a smaller effective sample size; however, the effective sample size in this study is consistent with the proportion of the total sample as observed in similar analyses in CLL.[26] While removing patients with extreme weights did not impact the results, there remains a limitation with lack of similarity of trials that led to these extreme weights. Therefore, these data alone preclude any definitive conclusions in the absence of randomized data and should be considered hypothesis generating findings warranting further study. Moreover, the covariates included in the analysis could not be individually evaluated due to the lack of patient-level data for venetoclax. In particular, minimal residual disease (MRD) could not be compared between trials given the lack of baseline covariates for the subgroup assessed for MRD in the venetoclax trial. The balancing exercise was limited to those factors reported in both trials and exclude both measured and unmeasured factors that may introduce bias. For example, the venetoclax cohort was enrolled to the trial from 2014 to 2016, whereas the pirtobrutinib cohort did not begin enrollment until November 2018 and follow-up continued during the COVID19 pandemic, which can have an effect on the incidence of adverse events. Moreover, the OS outcomes could potentially be influenced by the pre- and post-protocol therapies received. While these are not evaluable due to lack of reported data, there is the possibility of more frequent use of PI3K inhibitors during the time period of the

Jones et al trial, whereas the use of PI3Ki agents has become less common due to toxicity concerns since 2018.[27] Additionally, there may be some variability in the prior treatments received and other potentially prognostic variables, such as NOTCH1 mutation status, that could not be controlled by the reweighting exercise due to lack of data. The comparison of adverse events was also limited by the events reported by both trials. Furthermore, there may have been shifts in the care of patients between these non-contemporaneous trials, such as the time-limited use of venetoclax in combination with CD20 antibodies, that could have altered patient outcomes.

Despite the limitations of using a MAIC, this study provides initial insights and improves upon naïve indirect comparisons by adjusting for known cross-trial differences to suggest improved ORR, similar PFS and OS, and the favorable toxicity profile associated with pirtobrutinib. Patients who received cBTKi therapy are underrepresented in pivotal venetoclax studies, such as the MURANO trial, where less than 5% of patients had been exposed to BTK inhibitors before receiving venetoclax.[3] The selection of treatment after cBTKi failure is a clinically relevant question, since the use of BTK inhibitors is widely established in most routine healthcare settings and post-BTKi salvage strategies remain understudied. This study provides data to inform treatment choice in a setting where little data exist.

Conclusion

In summary, this MAIC found that ORR of pirtobrutinib was higher and OS and PFS of pirtobrutinib was comparable to venetoclax monotherapy administered continuously until progression in patients with relapsed or refractory CLL previously treated with a cBTKi. Pirtobrutinib was also associated with a generally better toxicity profile compared to venetoclax, suggesting it may be an effective treatment option for patients who are venetoclax-naïve after progressing on a cBTKi.

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Table 1. Study cohorts used in the matching adjusted indirect comparison

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	Pirtobrutinib (weighted) (N=146)[a]
Median age, years	66	69	66.5
Patients with >4 prior lines (%)	50.0%[b]	19.9%[c]	50.0%
BTKi discontinuation due to progression (%)	54.9%	71.9%	54.9%
del(11)(q22.3) present (%)	33.0%	17.8%	33.0%
del(17(p13.1) present (%)	46.7%	21.9%	46.7%
TP53 mutation present (%)	33.3%	35.6%	39.6%
Unmutated IGHV (%)	74.6%	66.4%	74.6%
ECOG PS, 0-1 (%)[d]	91.2%	94.5%	91.2%
Bulky disease (≥5cm)[d]	39.5%	28.1%	33.3%
Male sex (%)[d]	70.3%	68.5%	70.3%

ECOG PS=Eastern Cooperative Oncology Group performance status; IGHV= immunoglobulin heavy-chain variable region gene

[a] All patients were included in the weighted analyses; however, reweighting resulted in an effective sample size of 61

[b] Median (range) number of prior lines of therapy = 4 (1-15)

[c] Median (range) number of prior lines of therapy = 3 (1-9)

[d] Included in sensitivity analyses only

Table 2. iwCLL response (%)

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	unweighted OR (95% CI), p-value	Pirtobrutinib (weighted)	weighted OR (95% CI), p-value
ORR	64.8%	69.9%	1.26 (0.69-2.27), p=0.50	80.2%	2.22 (1.16-4.29), p=0.01
CR/CRi	8.8%	1.4%		0.5%	
PR	52.7%	67.8%		77.9%	
SD	24.2%	19.9%		10.7%	
PD	5.5%	2.7%		5.6%	

OR=odds ratio; CI=confidence interval; ORR=objective response rate; CR=complete response; CRi=CR with incomplete bone marrow recovery; PR=partial response; SD=stable disease; PD=progressive disease

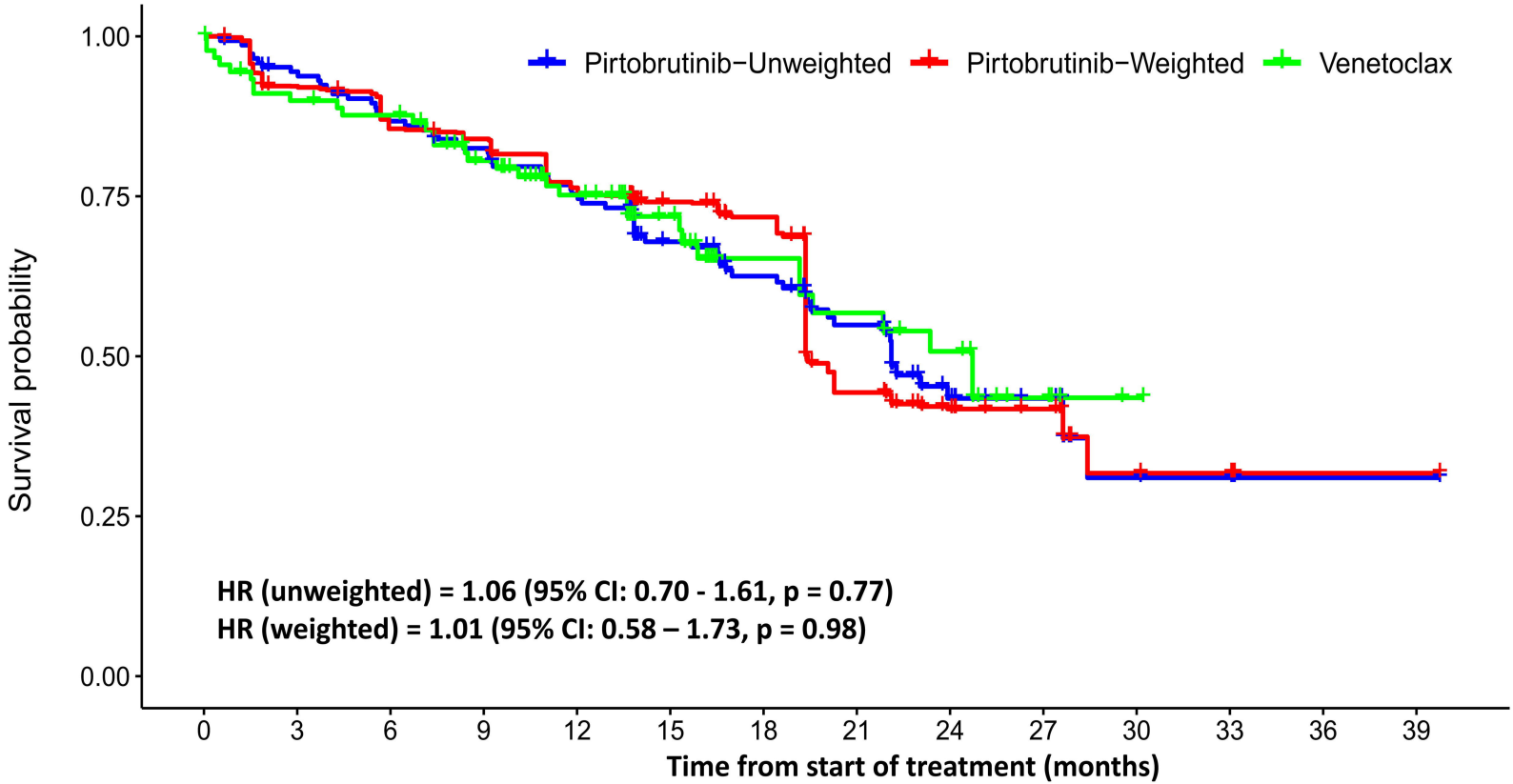
Table 3. Percent of patients with grade ≥3 adverse events

	Venetoclax (N=91)	**Pirtobrutinib (unweighted) (N=146)**	**Unweighted OR (95% CI), p-value**	**Pirtobrutinib (weighted)**	**Weighted OR (95% CI), p-value**
Anemia	28.6%	5.5%	0.15 (0.05-0.35), p < 0.001	1.3%	0.04 (0.004-0.16), p < 0.001
Febrile neutropenia	13.2%	1.4%	0.09 (0.01-0.43), p < 0.001	1.4%	0.10 (0.01-0.47), p < 0.001
Neutropenia	50.5%	19.9%	0.24 (0.13-0.45), p < 0.001	20.3%	0.25 (0.13-0.47), p < 0.001
Thrombocytopenia	28.6%	1.4%	0.04 (0.004-0.15), p < 0.001	1.1%	0.02 (0.00-0.12), p < 0.001
Pneumonia	6.6%	5.5%	0.82 (0.24-2.98), p = 0.78	1.2%	0.22 (0.02-1.25), p = 0.06
Treatment discontinuation due to adverse events	6.6%	7.5%	1.15 (0.37-3.95), p = 1.00	2.9%	0.44 (0.09-1.92), p = 0.32

Figure Legends

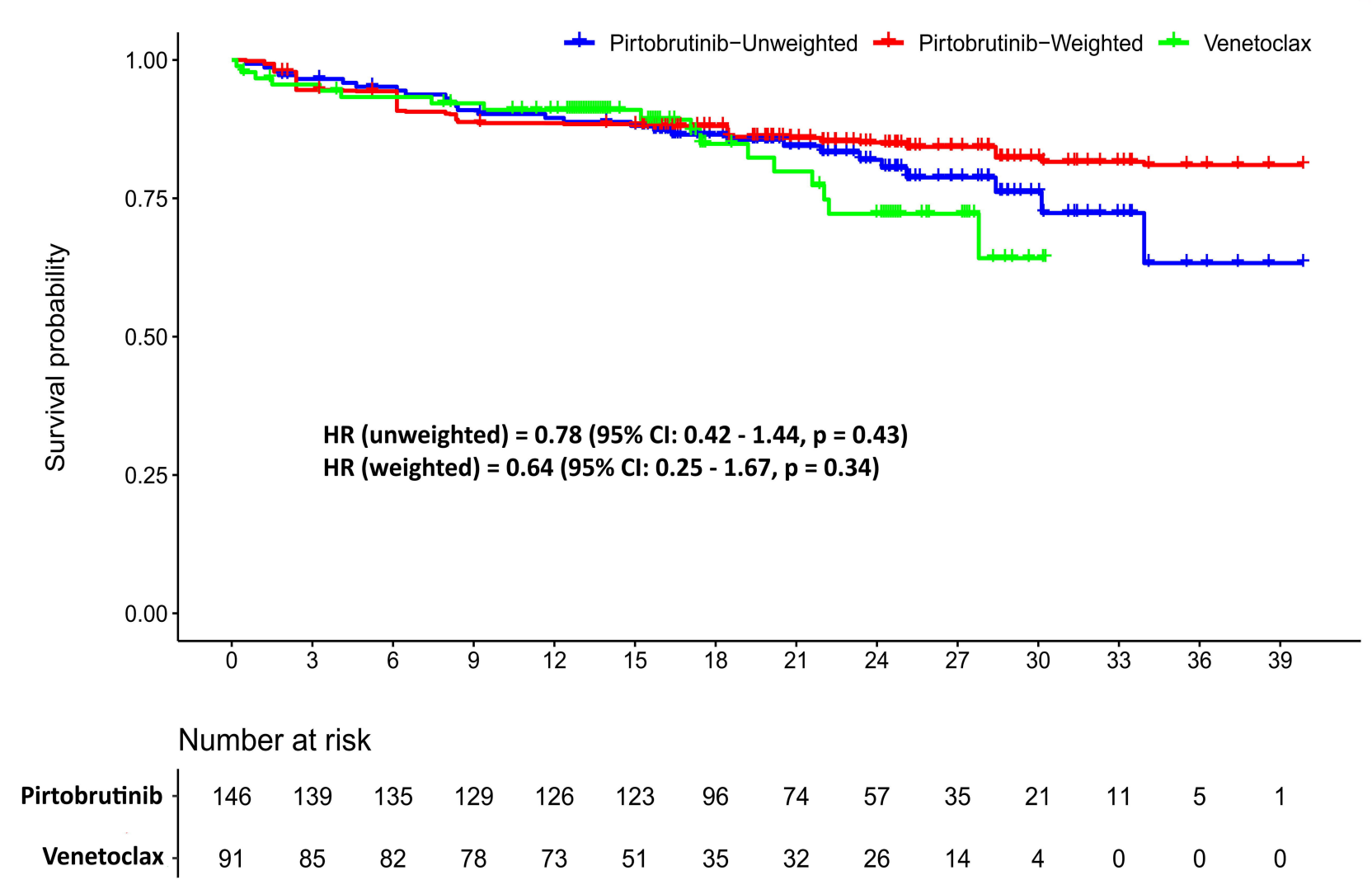
Figure 1. Progression-free survival

Figure 2. Overall survival



Number at risk

Pirtobrutinib	146	135	123	116	105	80	66	46	23	18	5	4	1	1
Venetoclax	91	80	77	65	53	35	23	20	16	7	3	0	0	0


Pirtobrutinib−Unweighted
Pirtobrutinib−Weighted
Venetoclax
Survival probability
1.00
0.75
0.50
0.25
0.00
HR (unweighted) = 0.78 (95% CI: 0.42 - 1.44, p = 0.43)
HR (weighted) = 0.64 (95% CI: 0.25 - 1.67, p = 0.34)
0 3 6 9 12 15 18 21 24 27 30 33 36 39
Number at risk
Pirtobrutinib 146 139 135 129 126 123 96 74 57 35 21 11 5 1
Venetoclax 91 85 82 78 73 51 35 32 26 14 4 0 0 0

Supplementary content: Sensitivity analyses

An unanchored MAIC relies on the assumption of conditional constancy of relative effects and assume that the relative treatment effects are constant between studies.[19] Meeting this stringent assumption is extremely difficult for all MAIC analysis; therefore, to achieve reliable predictions, adjustment methods in these studies should account for all effect modifiers and prognostic variables.[28] Therefore, for the unanchored MAIC, unbalanced prognostic factors may contribute to the outcome and thus become confounders. As a result, it was crucial that all factors that directly or indirectly affect outcomes by impacting the effect the treatment has on that outcome (e.g., including even the non-effect-modifying prognostic factors) were balanced. The primary analysis utilized an informed covariate approach. To ensure that this did not introduce bias into the study findings, sensitivity analyses were conducted balancing the cohorts on all available baseline factors (the primary covariates listed above plus the additional covariates of ECOG performance status 0/1 versus 2, percent of patients with bulky disease, and patient sex) to evaluate the potential impact of informed versus uninformed covariate selection. Additional sensitivity analyses were conducted in the case of the identification of extreme weights, where those patients were excluded, and analyses were re-run for each efficacy outcome.

Supplementary Table 1. Search strategy terms used to identify trials of venetoclax

A systematic literature review was conducted in MedLine, EMBASE, EBM Reviews, clinicaltrials.gov, and a series of conference proceedings through June 2022. Studies were included in this review if they enrolled patients with CLL who had prior cBTKi exposure, and if at least one clinical outcome of overall survival (OS), PFS, or tumor response (including ORR) were reported.

S.No.	Search strings
1.	lymphoma, non-hodgkin/
2.	(chronic lymphocytic leukemia or chronic lymphocytic leukaemia).mp.
3.	chronic lymphatic leukemia.mp.
4.	(chronic lymphocytic or CLL).mp.
5.	(small lymphocytic lymphoma or small-lymphocytic lymphoma).mp.
6.	small lymphocytic lymphoma.mp.
7.	(small lymphocytic or SLL).mp.
8	((chronic or small) adj3 (lymph* or leuk* or NHL)).mp.
9	(chronic lymphocytic leukemia or small lymphocytic lymphoma).mp.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	exp salvage therapy/
12	((salvage adj3 (chemotherap* or treatment* or therap*)) or (resistant adj3 (chemotherap* or treatment resistant))).mp.
13	(second line or 2nd line or 2?nd line or second-line or (second adj4 line)).ti,ab.
14	(third line or third-line or 3?rd line or 3rd line or (third adj4 line)).ti,ab.
15	(refractory or refractor* or relaps* or recurrent or (previously adj3 treated or previous* adj3 treat*) or (drug adj3 resistan*) or pre-treated or pretreated).ti,ab.
16	((failed or failure or discontinue or discontinu*) and (treatment* or therap* or prior or previous)).mp.
17	((chemotherap* or treatmen* or regime* or medication* or therap*) adj7 (refractory or recurrent or resistant or rescue or salvage or failed or failure)).mp.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	10 AND 18
20	Bruton Tyrosine Kinase inhibitor.mp.
21	(bruton's tyrosine kinase inhibitor or bruton tyrosine kinase inhibitor or bruton s tyrosine kinase inhibitor or inhibitor of bruton s tyrosine kinase inhibitor or inhibitor of bruton's tyrosine kinase inhibitor or inhibitor of bruton tyrosine kinase inhibitor or BTK inhibitors or BTKI or BTKi or BTKinhibitors or BTK?inhibitors or BTK).mp.
22	exp Agammaglobulinaemia Tyrosine Kinase/
23	(ibrutinib or imbruvica or "cra 032765" or cra032765 or cra-032765 or "pci 32765" or pci32765 or "pci 32765-00" or "pci 32765 00" or pci3276500 or PC-32765 or PC32765 or "PC 32765").mp.
24	(acalabrutinib or "calquence acp 196" or acp196 or acp-196 or Acp-196).mp.
25	(zanubrutinib or brukinsa or BGB-3111 or Bgb-3111 or "BGB 3111" or BGB3111).mp.
26	(Tirabrutinib or GS-4059 or Gs-4059 or "GS 4059" or GS4059 or ONO-4059 or Ono-4059 or ONO4059 or "ONO 4059").mp.

S.No.	Search strings
27	(pirtorutinib or LOXO-305 or "LOXO 305" or Loxo-305 or "Loxo 305" or LY-3527727 or "LY 3527727" or LY3527727 or RXC-005 or RXC005 or "RXC 005").mp.
28	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	19 AND 28
30	exp adolescent/ or exp child/ or exp infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or child* or girl? or infant* or juvenil* or kid? or minors or minors* or neonat* or neonat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf.
31	(Comment or Letter or Editorial or Case Reports or Review or Practice Guideline).pt.
32	(nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.
33	29 not (30 or 31 or 32)
34	(venetoclax or “BCL-2” or BCL2).ti.ab
35	33 and 34

Supplementary Table 2. Venetoclax trials identified in the literature review and eligibility assessment

A total of 14 publications representing 8 single-arm trials were identified.

Citation	Population	Intervention	Outcomes	Included or Excluded (with reason)
Jones, Mato et al. 2018[9] NCT02141282	91 patients who received venetoclax after ibrutinib	Venetoclax initiated at 20 mg daily, intra-patient ramp-up to 400 mg daily.	ORR/tumor response DOR PFS OS Safety	Included
Anderson, Tan et al. 2017[28] NCT01328626, NCT01889186, and/or NCT01682616	67 heavily pre-treated patients enrolled to various early phase trials	Venetoclax (n=51 monotherapy; n=16 venetoclax+rituximab,)	Time to progression Post-venetoclax outcomes	Excluded (Data were combined between monotherapy and combined therapy regimens)
Blombery, Thompson et al. 2020; 2022[29,30]	92/89 patients enrolled to various clinical trials	Venetoclax (trials not specified)	BAX mutations	Excluded (No efficacy or safety outcomes reported)
Coutre, Choi et al 2018[31] NCT02141282	36 patients who received venetoclax after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response MRD Safety	Excluded (same study as Jones at al, 2018 but limited to post-idelalisib which is not comparable to BRUIN)
Coutre, Wierda et al 2016[32] NCT02141282	38 patients who received venetoclax after ibrutinib, 10 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Davids, Hallek et al 2018[33] NCT01328626, NCT01889186, NCT02141282	350 patients enrolled to various phase 1/2 clinical trials	400 mg daily venetoclax monotherapy	Safety	Excluded (No efficacy outcomes reported)
Jones, Mato et al. 2015[34] NCT02141282	22 patients who received venetoclax after ibrutinib, 6 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)

Jones, Choi et al 2016[35]	43 patients who received venetoclax after ibrutinib, 21 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Jones, Wierda et al 2016[36]	41 patients who received venetoclax after ibrutinib, 13 after idealisib	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response Safety	Excluded (Same study as Jones et al. 2018)
Murayama, Izutsu et al 2021[37] NCT0226573	12 Japanese patients with R/R CLL/SLL	Patients enrolled in phase 1 received 400 mg/day venetoclax monotherapy. Patients enrolled in phase 2 received 400 mg/day venetoclax, plus rituximab.	ORR in phase 2 only Safety	Excluded (Phase 1 data only for venetoclax monotherapy)
Roberts, Seymour et al 2016[8,38] NCT02141282, NCT01 889186, NCT01328626, and/or NCT01682616	387 patients enrolled to various phase 1/2 clinical trials	Venetoclax monotherapy Venetoclax + rituximab Venetoclax doses ranged from 150 mg/day to 1200 mg/day	ORR/tumor response MRD DOR PFS	Excluded (Data were combined between monotherapy and combined therapy regimens)
Roberts, Davis et al. 2016[39] NCT01328626	166 patients with R/R CLL	Phase 1 dose escalation phase, phase 2 expansion phase-weekly stepwise ramp-up in doses as high as 400 mg per day	ORR/response Safety PFS DOR	Excluded (Phase 1 data only for venetoclax monotherapy)
Stilginbauer, Eichorst et al 2016[40] NCT01889186	107 patients with R/R CLL	Once daily venetoclax with a weekly dose ramp-up schedule (20, 50, 100, 200, 400 mg) over 4–5 weeks, ramp up to 400 mg daily	ORR/response Safety PFS OS	Excluded (Phase 1 data only for venetoclax monotherapy)
Wierda, Davids et al, 2017[41]	28 patients who received venetoclax after more than one prior BCRi (including ibrutinib, idelalisib, and investigational agents).	Venetoclax initiated at 20 mg daily, intrapatient ramp-up to 400 mg daily.	ORR/tumor response PFS OS Safety	Excluded (Same study as Jones et al. 2018)

MAIC=matching adjusted indirect comparison; CLL=chronic lymphocytic leukemia; ORR=objective response rate; DOR=duration of response; PFS=progression-free survival; OS=overall survival; BCRi = B-cell receptor pathway inhibitors

Supplementary Table 3. Prior therapies received by patients included in this analysis

Prior Systemic Therapies, n (%)	**Venetoclax (N=91)**	**Pirtobrutinib (N=146)**
Prior BTK	91 (100.0)	146 (100.0)
Prior anti-CD20 Antibody	Not reported	120 (82.2)
Prior Chemotherapy	Not reported	108 (74.0)
Prior PI3K Agent	11 (12.1)	17 (11.6)
Prior Lenalidomide	Not reported	11 (7.5)
Prior CAR-T	Not reported	2 (1.4)
Other Systemic Therapy	Not reported	24 (16.4)

Supplementary Table 4. Sensitivity analyses using all available baseline covariates

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	Unweighted OR/HR (95% CI), p-value	Pirtobrutinib (weighted)	Weighted OR/HR (95% CI), p-value
Clinical outcomes					
ORR (%)	64.8	69.9	1.26 (0.69-2.27), p = 0.47	84.2	2.88 (1.46-5.76), p = 0.001
PFS, median (95% CI) months	24.7 (19.2 - NE)	22.1 (19.5 - NE)	1.06 (0.70-1.61), p = 0.77	19.4 (18.6 – NE)	1.15 (0.66-2.01), p=0.62
OS, median (95% CI) months	NE (27.8 - NE)	NE (33.9 - NA)	0.78 (0.42-1.44), p = 0.43	NE (NE-NE)	0.88 (0.34-2.29), p = 0.78
Safety outcomes, grade ≥3 (%)					
Anemia	28.6	5.5	0.15 (0.05-0.35), p<0.001	1.1	0.04 (0.00-0.16), p<0.001
Febrile neutropenia	13.2	1.4	0.09 (0.01-0.43), p < 0.001	1.8	0.10 (0.01-0.47), p < 0.001
Neutropenia	50.5	19.9	0.24 (0.13-0.45), p<0.001	21.3	0.26 (0.14-0.49), p<0.001
Thrombocytopenia	28.6	1.4	0.04 (0.00-0.15), p<0.001	1.8	0.04 (0.00-0.16), p<0.001
Pneumonia	6.6	5.5	0.82 (0.24-2.98), p = 0.78	0.8	0.11 (0.00-0.92), p = 0.02
Treatment discontinuation due to adverse events	6.6	7.5	1.15 (0.37-3.95), p = 1.00	2.6	0.44 (0.09-1.92), p = 0.32

NE=not evaluable

Supplementary Table 5. Percent of patients with any grade treatment-emergent adverse events

	Venetoclax (N=91)	Pirtobrutinib (unweighted) (N=146)	Unweighted OR (95% CI), p-value	Pirtobrutinib (weighted)	Weighted OR (95% CI), p-value
Anemia	52.7	11.0	0.11 (0.05-0.22), <0.001	5.1	0.05 (0.02-0.12), <0.001
Febrile neutropenia	13.2	1.4	0.09 (0.01- 0.43), <0.001	1.4	0.10 (0.01 – 0.47), <0.001
Neutropenia	61.5	26.7	0.23 (0.13-0.41), <0.001	29.4	0.26 (0.14 – 0.47), <0.001
Thrombocytopenia	47.3	3.4	0.04 (0.01 – 0.11), <0.001	2.3	0.03 (0.004 – 0.09), <0.001
Pneumonia	11.0	10.3	0.93 (0.37 – 2.43), 1.0	3.9	0.32 (0.08-1.07), 0.05

Supplementary Table 6. Listing of number (%) of all adverse events reported similarly from both trials

	Venetoclax(n=91)					Pirtobrutinib (n=146)				
n (%)	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Total	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Total
Blood and lymphatic system disorders										
Anaemia	22 (24)	26 (29)	0	0	48 (53)	8(5.5)	8(5.5)	0(0.0)	0(0.0)	16(11.0)
Febrile neutropenia	1 (1)	11 (12)	0	0	12 (13)	0(0.0)	2(1.4)	0(0.0)	0(0.0)	2 (1.4)
Neutropenia	10 (11)	18 (20)	28 (31)	0	56 (62)	5(3.4)	6 (4.1)	6 (4.1)	0(0.0)	17(11.6)
Thrombocytopenia	17 (19)	11 (12)	15 (17)	0	43 (47)	3(2.1)	1 (0.7)	1(0.7)	0(0.0)	5(3.4)
Cardiac Disorders										
Atrial fibrillation	0	1 (1)	0	0	1 (1)	4(2.7)	1(0.7)	1(0.7)	0(0.0)	6(4.1)
Myocardial infarction[a]	0	1 (1)	0	0	1 (1)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Pericardial effusion	0	1 (1)	0	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Ear and labyrinth disorders										
Cataract	0	2 (2)	0	0	2 (2)	1 (0.7)	1 (0.7)	0(0.0)	0(0.0)	2(1.4)
Gastrointestinal disorders										
Abdominal pain	15 (17)	4 (4)	0	0	19 (21)	25(17.1)	2(1.4)	0(0.0)	0(0.0)	27(18.5)
Constipation	19 (21)	0	0	0	19 (21)	27(18.5)	1(0.7)	0(0.0)	0(0.0)	28(19.2)
Diarrhoea	41 (45)	6 (7)	0	0	47 (52)	41(28.1)	1(0.7)	0(0.0)	0(0.0)	42(28.8)
Dysphagia	4 (4)	1 (1)	0	0	5 (6)	7(4.8)	0(0.0)	0(0.0)	0(0.0)	7(4.8)
Haemorrohoids	3 (3)	1 (1)	0	0	4 (4)	4(2.7)	0(0.0)	0(0.0)	0(0.0)	4(2.7)
Intestinal obstruction[b]	0	1 (1)	0	0	1 (1)	0(0.0)	1(0.7)	0(0.0)	0(0.0)	1(0.7)
Nausea	51 (56)	1 (1)	0	0	52 (57)	27(18.5)	0(0.0)	0(0.0)	0(0.0)	27(18.5)
Small intestinal obstruction	1 (1)	1 (1)	0	0	2 (2)	0(0.0)	1(0.7)	0(0.0)	0(0.0)	1(0.7)
Stomatitis	8 (9)	1 (1)	0	0	9 (10)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Vomiting	20 (22)	1 (1)	0	0	21 (23)	12(8.2)	0(0.0)	0(0.0)	0(0.0)	12(8.2)
General disorders and administration site conditions										
Asthenia	3 (3)	1 (1)	0	0	4 (4)	4(2.7)	0(0.0)	0(0.0)	0(0.0)	4(2.7)
Chills	10 (11)	1 (1)	0	0	11 (12)	6(4.1)	1(0.7)	0(0.0)	0(0.0)	7(4.8)
Fatigue	33 (36)	4 (4)	2 (2)	0	39 (43)	43(29.5)	1(0.7)	0(0.0)	0(0.0)	44(30.1)
Multi-organ failure[c]	0	0	0	1 (1)	1 (1)	0(0.0)	0(0.0)	1(0.7)	0(0.0)	1(0.7)
Peripheral oedema	21 (23)	0	0	0	21 (23)	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(2.1)
Pyrexia	17 (19)	1 (1)	0	0	18 (20)	13 (8.9)	1 (0.7)	0 (0.0)	0 (0.0)	14 (9.6)
Infections and infestations										
Bacteraemia	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	1(0.7)	0(0.0)	2(1.4)
Bronchitis	5 (5)	1 (1)	0	0	6 (7)	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(2.1)
Cellulitis	2 (2)	3 (3)	0	0	5 (5)	3(2.1)	1(0.7)	0(0.0)	0(0.0)	4(2.7)
Diverticulitis	2 (2)	1 (1)	0	0	3 (3)	1(0.7)	1(0.7)	0 (0.0)	0(0.0)	2(1.4)
Viral gastroenteritis	2 (2)	1 (1)	0	0	3 (3)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Laryngitis[d]	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Pneumonia	4 (4)	5 (5)	1 (1)	0	10 (11)	7(4.8)	7(4.8)	0(0.0)	1(0.7)	15 (10.3)
Septic shock	0	0	0	1 (1)	1 (1)	0(0.0)	0 0.0)	2(1.4)	1(0.7)	3(2.1)
Upper respiratory tract infection[e]	24 (26)	0	0	0	24 (26)	31(21.2)	0(0.0)	0(0.0)	0(0.0)	31(21.2)
Urinary tract infection	6 (7)	1 (1)	1 (1)	0	8 (9)	17(11.6)	4 (2.7)	0(0.0)	0(0.0)	21(14.4)
Staphylococcal wound infection[f]	0	1 (1)	0	0	1 (1)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Injury, poising, and procedural complications										
Bruising[g]	15 (17)	0	0	0	15 (17)	32 (21.9)	0(0.0)	0(0.0)	0(0.0)	32(21.9)
Fall	2 (2)	3 (3)	0	0	5 (6)	20(13.7)	0(0.0)	0(0.0)	0(0.0)	20(13.7)
Investigations										
Increased alanine aminotransferase	11 (12)	2 (2)	1 (1)	0	14 (15)	2(1.4)	1 0.7)	0(0.0)	0(0.0)	3(2.1)
Increased aspartate aminotransferase	16 (18)	0	2 (2)	0	18 (20)	5(3.4)	0(0.0)	0(0.0)	0(0.0)	5(3.4)
Increased blood bilirubin	11 (12)	1 (1)	0	0	12 (13)	8 (5.5)	1 (0.7)	0(0.0)	0(0.0)	9 (6.2)
Decreased lymphocyte count	9 (10)	11 (12)	3 (3)	0	23 (25)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Increased lymphocyte count	4 (4)	4 (4)	0	0	8 (9)	3 (2.1)	1 (0.7)	0(0.0)	0(0.0)	4 (2.7)
Metabolism and nutrition disorders										
Dehydration	6 (7)	2 (2)	0	0	8 (9)	1(0.7)	3(2.1)	0(0.0)	0(0.0)	4 (2.7)
Hyperglycaemia	5 (5)	4 (4)	1 (1)	0	10 (11)	4 (2.7)	1(0.7)	0(0.0)	0(0.0)	5 (3.4)
Hyperkalaemia	13 (14)	1 (1)	0	0	14 (15)	6 (4.1)	0(0.0)	0(0.0)	0(0.0)	6 (4.1)
Hypermagnesaemia	1 (1)	1 (1)	0	0	2 (2)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Hyperphosphataemia	11 (12)	0	0	0	11 (12)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Hyperuricaemia	12 (13)	0	0	0	12 (13)	20 (13.7)	0(0.0)	0(0.0)	0(0.0)	20 (13.7)
Hypoalbuminaemia	13 (14)	2 (2)	0	0	15 (17)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.7)
Hypokalaemia	15 (16)	5 (5)	0	0	20 (22)	5 (3.4)	2(1.4)	0(0.0)	0(0.0)	7 (4.8)

Hyponatraemia	11 (12)	6 (7)	0	0	17 (19)	1 (0.7)	1 (0.7)	0(0.0)	0(0.0)	2 (1.4)
Hypophosphataemia	5 (5)	11 (12)	1 (1)	0	17 (19)	2(1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Musculoskeletal and connective tissue disorders										
Arthralgia	16 (18)	0	0	0	16 (18)	26 (17.8)	1(0.7)	0(0.0)	0(0.0)	27 (18.5)
Arthritis	1 (1)	1 (1)	0	0	2 (2)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)
Back pain	16 (18)	0	0	0	16 (18)	26 (17.8)	1(0.7)	0(0.0)	0(0.0)	27 (18.5)
Intervertebral disc protrusion	0	1 (1)	0	0	1 (1)	3 (2.1)	1 (0.7)	0(0.0)	0(0.0)	4 (2.7)
Extremity pain	12 (13)	0	0	0	12 (13)	12 (8.2)	0(0.0)	0(0.0)	0(0.0)	12 (8.2)
Spinal column stenosis	0	1 (1)	0	0	1 (1)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Neoplasms benign, malignant, and unspecified										
Prostate cancer	1 (1)	1 (1)	0	0	2 (2)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Squamous cell carcinoma of skin	5 (5)	1 (1)	0	0	6 (6)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Nervous system disorders										
Dizziness	12 (13)	0	0	0	12 (13)	25 (17.1)	0(0.0)	0(0.0)	0(0.0)	25 (17.1)
Headache	18 (20)	1 (1)	0	0	19 (21)	26 (17.8)	0(0.0)	0(0.0)	0(0.0)	26 (17.8)
Spinal cord compression[h]	0	1 (1)	0	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Presyncope	2 (2)	0	1 (1)	0	3 (3)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Syncope	0	2 (2)	0	0	2 (2)	0(0.0)	3 (2.1)	0(0.0)	0(0.0)	3 (2.1)
Renal and urinary disorders										
Acute kidney injury	2 (2)	1 (1)	0	0	3 (3)	0(0.0)	5 (3.4)	1 (0.7)	0 (0.0)	6 (4.1)
Nephrolithiasis	0	1 (1)	0	0	1 (1)	0(0.0)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)
Respiratory, thoracic, and mediastinal disorders										
Cough	24 (26)	0	0	0	24 (26)	41 (28.1)	0(0.0)	0(0.0)	0(0.0)	41 (28.1)
Dyspnoea	12 (13)	2 (2)	0	0	14 (15)	25 (17.1)	1 (0.7)	0(0.0)	0(0.0)	26 (17.8)
Hypoxia	0	4 (4)	0	0	4 (4)	1 (0.7)	2 (1.4)	0(0.0)	0(0.0)	3 (2.1)
Oropharyngeal pain	11 (12)	0	0	0	11 (12)	9 (6.2)	0(0.0)	0(0.0)	0(0.0)	9 (6.2)
Pleural effusion	3 (3)	1 (1)	0	0	4 (4)	4 (2.7)	0(0.0)	1(0.7)	0(0.0)	5 (3.4)
Pulmonary oedema	0	0	1 (1)	0	1 (1)	1 (0.7)	0(0.0)	0(0.0)	0(0.0)	1 (0.7)
Respiratory failure	0	0	1 (1)	0	1 (1)	0(0.0)	0(0.0)	1 (0.7)	1 (0.7)	2 (1.4)
Wheezing	3 (3)	1 (1)	0	0	4 (4)	2 (1.4)	0(0.0)	0(0.0)	0(0.0)	2 (1.4)
Skin and subcutaneous tissue disorders										
Rash	11 (12)	0	0	0	11 (12)	6 (4.1)	0(0.0)	0(0.0)	0(0.0)	6 (4.1)
Vascular disorders										
Hypertension	5 (5)	6 (7)	0	0	11 (12)	21 (14.4)	4(2.7)	0(0.0)	0(0.0)	25 (17.1)
Hypotension	1 (1)	1 (1)	0	0	2 (2)	3 (2.1)	3(2.1)	0(0.0)	0(0.0)	6 (4.1)

Pirtobrutinib reported as: [a]acute myocardial infarction; [b]large intestinal obstruction; [c]multiple organ dysfunction; [d]reflux laryngitis; [e]respiratory tract infection; [f]staphylococcal skin infection; [g]contusion; [h]nerve compression