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

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Abstract

Venetoclax is a standard treatment for patients with chronic lymphocytic leukemia (CLL) following covalent Bruton tyrosine kinase 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-pretreated CLL. Data from patients with CLL who were venetoclax-naïve and pretreated with cBTKi received pirtobrutinib (N=146) in the phase I/II 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. 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% confidence interval [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 treatment-emergent adverse events were lower in weighted analyses for pirtobrutinib *versus* 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 anal-

yses 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 pretreated 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 wild-type 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 III trials for patients with CLL (*clinicaltrials gov. Identifier: 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 I/II BRUIN trial (*clinicaltrials.gov Identifier: 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 three prior lines of therapy (at least 1 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, *clinicaltrials gov. Identifier: 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 (*Online Supplementary Tables S1* and *S2*). One study met eligibility criteria (*clinicaltrials gov. Identifier: 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. The following outcomes were reported in both trials and included in the MAIC: ORR by investigator assessment; PFS; OS; treatment-emergent adverse events (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 clinicaltrials gov. Identifier: 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 TEAE 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 *Online Supplementary Appendix*.

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 *Online Supplementary Table S3*. 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% confidence interval [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, six 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 International Workshop on CLL 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 odds ratio [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 (*Online Supplementary Table S5*). 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 *Online Supplementary Table S6*, which reports details of events

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

Characteristic	Venetoclax N=91	Pirtobrutinib (unweighted) N=146	Pirtobrutinib (weighted)[a]
Median age in 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(17p13.1) 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

[a]All patients were included in the weighted analyses; however, reweighting resulted in an effective sample size of 61. [b]Median number of prior lines of therapy =4 (range, 1-15). [c]Median number of prior lines of therapy =3 (range, 1-9). [d]Included in sensitivity analyses only. BTKi: Bruton tyrosine kinase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; *IGHV*: immunoglobulin heavy-chain variable region gene.

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 (*Online Supplementary Table S4*). 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*).
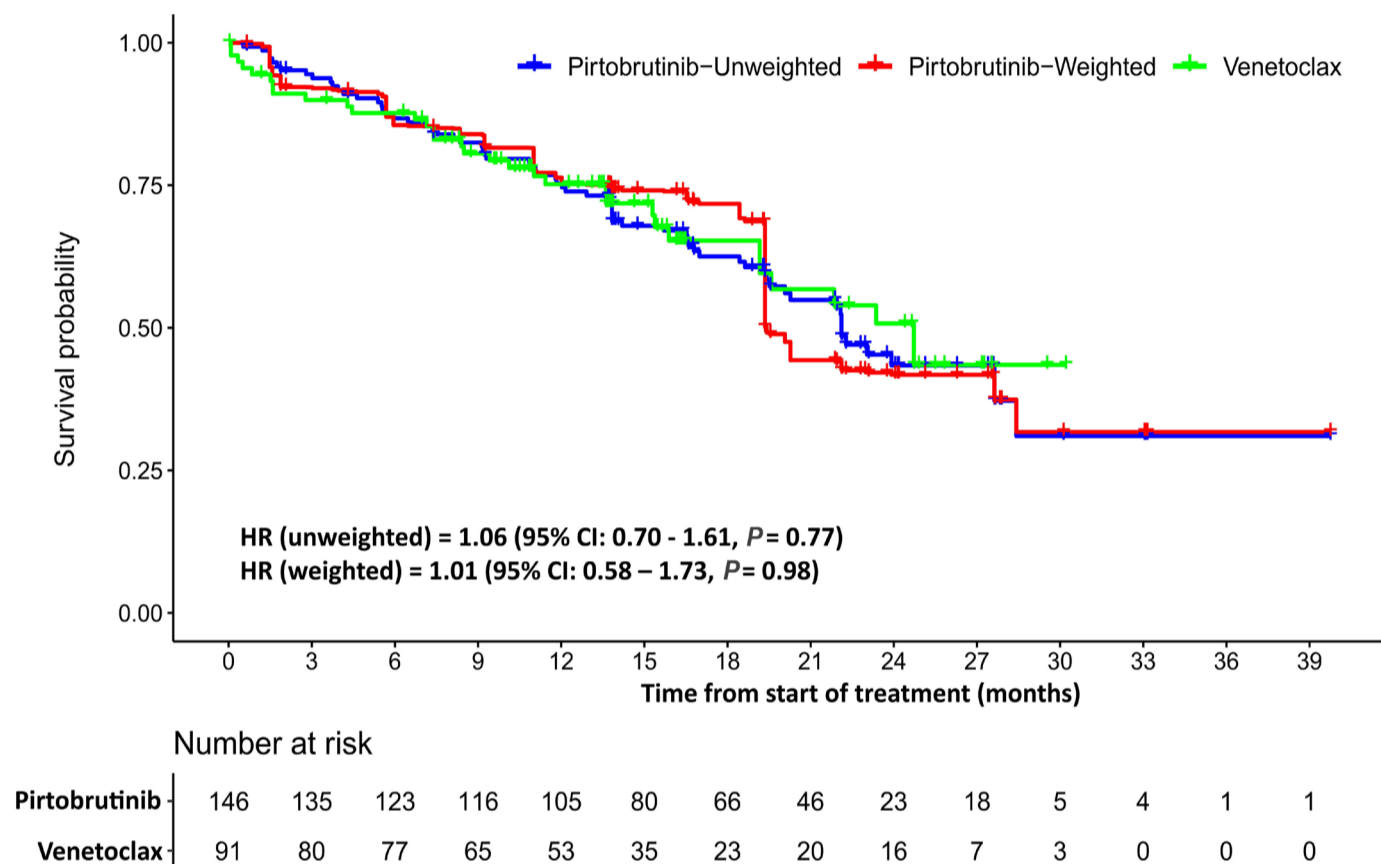

HR (unweighted) = 1.06 (95% CI: 0.70 - 1.61, *P* = 0.77)
HR (weighted) = 1.01 (95% CI: 0.58 − 1.73, *P* = 0.98)

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39
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

Figure 1. Progression-free survival. HR: hazard ratio; CI: confidence interval.

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)

Number at risk

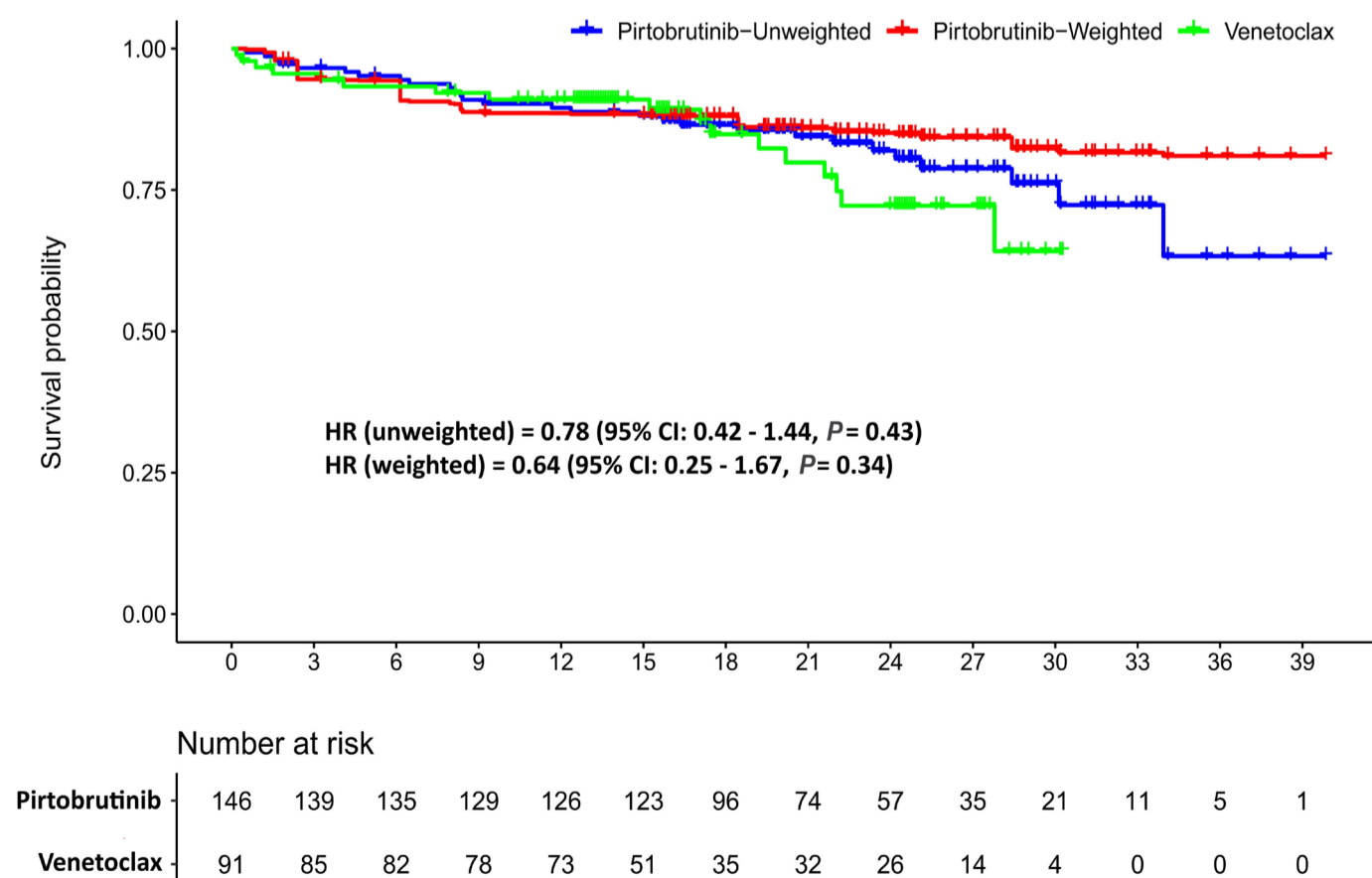|	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Pirtobrutinib	146	139	135	129	126	123	96	74	57	35	21	11	5	1
Venetoclax	91	85	82	78	73	51	35	32	26	14	4	0	0	0

Figure 2. Overall survival. HR: hazard ratio; CI: confidence interval.

Table 2. International Workshop on Chronic Lymphocytic Leukemia response (%).

iwCLL response	Venetoclax % N=91	Pirtobrutinib % (unweighted) N=146	Unweighted OR (95% CI), P	Pirtobrutinib % (weighted)[a]	Weighted OR (95% CI), P
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	-

[a]All patients were included in the weighted analyses; however, reweighting resulted in an effective sample size of 61. IwCLL: International Workshop on Chronic Lymphocytic Leukemia; 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.

Adverse event	Venetoclax % N=91	Pirtobrutinib % (unweighted) N=146	Unweighted OR (95% CI), P	Pirtobrutinib % (weighted)[a]	Weighted OR (95% CI), P
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

[a]All patients were included in the weighted analyses; however, reweighting resulted in an effective sample size of 61. OR: odds ratio; CI: confidence interval.

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] 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 dura-

tion of venetoclax in addition to rituximab, only included five 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, eight patients with CLL and two 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 seven of the ten 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.

Disclosures

Contributions

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Data-sharing statement

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