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Matching-Adjusted Indirect Comparison of Pirtobrutinib vs Venetoclax Continuous Monotherapy in Patients with Relapsed/Refractory CLL Previously Treated with a Covalent BTK Inhibitor

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Background

- Pirtobrutinib, a highly selective non-covalent (reversible) Bruton tyrosine kinase inhibitor, is under investigation for the treatment of patients with CLL after exposure to one or more covalent Bruton tyrosine kinase inhibitors (cBTKi)
- The B-cell lymphoma 2 inhibitor (BCL2i), venetoclax, is a treatment option used for patients with CLL
- Despite the use of venetoclax in patients previously treated with cBTKi, little data exist to inform this practice
- This study was designed to compare pirtobrutinib to venetoclax in a matching adjusted indirect comparison (MAIC) in the post-cBTKi setting

Trial Data

Venetoclax study (NCT0214128)

- A systematic literature review was conducted and identified only one study of venetoclax monotherapy in the post-cBTKi setting
- Jones et al[1] was an interim analysis of a single-arm trial of venetoclax among the subgroup of patients with prior cBTKi therapy.
- Summary data were limited to those available in this publication; no updates to this interim analysis were available for analysis

Pirtobrutinib Study[2] (NCT0214128; BRUIN)

- Additional selection criteria were applied to limit the cohort to patients that would have been eligible for the venetoclax study:
  - Diagnosis of CLL
  - Prior cBTKi exposure
  - Excluded patients with prior BCL2i therapy or prior stem cell transplant

References

1. Jones JA, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *The Lancet. Oncology,* 2018. **19**(1): p. 65-75.
2. Mato AR, et al. Pirtobrutinib in Covalent BTK-Inhibitor Pre-treated CLL/SLL. *New England Journal of Medicine,* 2023. In press.
3. Signorovitch JE, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value in Health*, 2012. **15**(6): p. 940-947.
4. Guyot P, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology,* 2012. **12**(1): p. 1-13.

Statistical Methods

MAIC

- This MAIC followed accepted methods for the conduct of an unanchored analysis[3]
- Patient-level data from the pirtobrutinib study were re-weighted to match the venetoclax study with logistic regression using a method of moments approach
  - Covariates for reweighting were those that were reported in both studies: age, number of prior therapies, reason for cBTKi discontinuation, del(17p), TP53, del(11q), IGHV mutation.
    - Additional covariates were identified and included in sensitivity analyses: ECOG performance status, bulky disease, sex
  - Kaplan Meier curves from the venetoclax study were digitized using PlotDigitizer
    - The method by Guyot et al[4] was used to simulate patient-level data from the venetoclax trial for time-to-event outcomes

Outcomes Assessed

- Overall response rate (ORR) and each available treatment-emergent adverse event (TEAE)
  - Fisher's exact test
  - Reported as odds ratios, 95% confidence interval (CI), and level of statistical significance
- Progression-free (PFS) and overall survival (OS) were measured from time of study enrollment
  - Cox regression and log-rank tests and were reported as hazard ratio (HR), with corresponding 95% CI and level of statistical significance
- Both unadjusted and adjusted analyses were conducted for all outcomes

Results

Table 1. Cohort Characteristics

Characteristic	Venetoclax (N=91)	Pirtobrutinib (unadjusted) (N=146)	Pirtobrutinib (adjusted)
Median age, years	66	69	67.5
Patients with >4 prior lines (%)	50%[a]	20%[b]	50%
BTKi discontinuation due to progression (%)	55%	72%	55%
del(11)(q22.3) present (%)	33%	18%	33%
del(17(p13.1) present (%)	47%	22%	47%
TP53 mutation present (%)	33%	36%	33%
Unmutated IGHV (%)	75%	66%	75%
ECOG PS, 0-1 (%)[c]	91.2%	94.5%	91.2%
Bulky disease (≥5cm)[c]	40%	28%	40%

ECOG PS=Eastern Cooperative Oncology Group performance status; IGHV= immunoglobulin heavy-chain variable region gene; [a] Median (range) number of prior lines of therapy = 4 (1-15); [b] Median (range) number of prior lines of therapy = 3 (1-9); [c] Included in sensitivity analyses

Results

Table 2. Tumor Response

	Venetoclax (N=91)	Pirtobrutinib (unadjusted) (N=146)	Unadjusted OR (95% CI), p-value	Pirtobrutinib (adjusted)	Adjusted OR (95% CI), p-value
ORR	65%	70%	1.26 (0.69-2.27), p=0.50	80%	2.22 (1.16-4.29), p=0.01
CR/CRi	9%	1%		0%	
PR	53%	68%[a]		78%[a]	
SD	24%	20%		11%	
PD	5%	3%		6%	

ORR=objective response rate; CR=complete response; CRi=CR with incomplete bone marrow recovery; PR=partial response; SD=stable disease; PD=progressive disease; OR=odds ratio; CI: confidence interval; [a] Inclusive of PR-L (partial response with lymphocytosis)

Table 3. Treatment-Emergent Adverse Events

	Venetoclax (N=91)	Pirtobrutinib (unadjusted) (N=146)	Unadjusted OR (95% CI), p-value	Pirtobrutinib (adjusted)	Adjusted OR (95% CI), p-value
Anemia	29%	5%	0.15 (0.05-0.35), p<0.001	1%	0.04 (0.004-0.16), p<0.001
Febrile neutropenia	13%	1%	0.09 (0.01-0.43), p<0.001	1%	0.10 (0.01-0.47), p<0.001
Neutropenia	51%	20%	0.24 (0.13-0.45), p<0.001	20%	0.25 (0.13-0.47), p<0.001
Thrombo-cytopenia	29%	1%	0.04 (0.004-0.15), p<0.001	1%	0.02 (0.00-0.12), p<0.001
Pneumonia	7%	5%	0.82 (0.24-2.98), p=0.78	1%	0.22 (0.02-1.25), p=0.06
Treatment discontinuation due to adverse events	7%	8%	1.15 (0.37-3.95), p=1.0	3%	0.44 (0.09-1.92), p=0.32

Figure 1. Progression-Free Survival

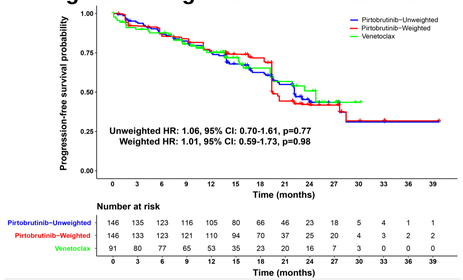
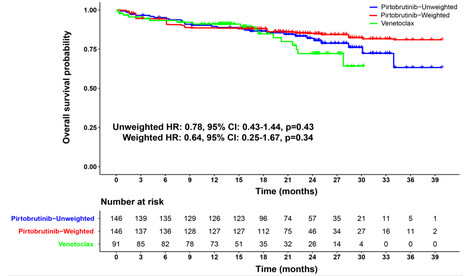


Figure 2. Overall Survival



Limitations

- Patient-level data were not available from the venetoclax study, so it remains unclear if the patients included in the analysis are truly similar
  - The covariates included in the analysis could not be individually evaluated due to the lack of patient-level data for venetoclax
- The reweighting exercise resulted in a smaller effective sample size and some extreme weights that could have impacted the analyses
- The balancing exercise was limited to those factors reported in both trials and exclude both measured and unmeasured factors that may introduce bias

Conclusions

- PFS and OS 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 associated with improved ORR and generally improved toxicity profile compared to venetoclax
- This study raises important questions regarding optimal treatment sequencing of pirtobrutinib and venetoclax in cBTKi-treated CLL
- These data are limited by the lack of prospective direct comparisons and lack of long-term follow-up, precluding definitive conclusions to be drawn from this work

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