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Pirtobrutinib Demonstrates Superior Relapse-Free and Overall Survival Compared with Idelalisib/Rituximab in CLL

A Propensity-Matched Real-World Analysis of the TriNetX Global Collaborative Network

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HEADLINE RESULTS

1:1 propensity-score–matched cohorts, 144 patients per arm

CLL RELAPSE

20.1% vs 47.2%

RR 0.43 (95% CI 0.30–0.62) · p < 0.001

Pirtobrutinib vs idelalisib + rituximab

ALL-CAUSE MORTALITY

18.1% vs 68.1%

RR 0.27 (95% CI 0.18–0.38) · p < 0.001

Pirtobrutinib vs idelalisib + rituximab

RELAPSE-FREE SURVIVAL

68.6% vs 31.3%

HR 0.58 (95% CI 0.37–0.91) · log-rank p = 0.016

Pirtobrutinib vs idelalisib + rituximab

OVERALL SURVIVAL

55.5% vs 18.9%

HR 0.62 (95% CI 0.39–0.99) · log-rank p = 0.045

Pirtobrutinib vs idelalisib + rituximab

BACKGROUND & AIM

Pirtobrutinib is a non-covalent Bruton tyrosine kinase (BTK) inhibitor that has demonstrated efficacy in BTK inhibitor–pretreated chronic lymphocytic leukemia (CLL). Idelalisib combined with rituximab is a mechanistically distinct, PI3K inhibitor–based regimen used in the same disease setting.

Evidence gap

Direct real-world comparative data for pirtobrutinib against PI3K inhibitor–based regimens such as idelalisib/rituximab remain limited. Large multicentre electronic health record (EHR) networks make it possible to compare these strategies in patients treated outside of clinical trials.

Study aim

To compare relapse and survival outcomes between adults with CLL who received pirtobrutinib and those who received idelalisib plus rituximab, using propensity score–matched cohorts drawn from a large multicentre EHR database.

THE TWO STRATEGIES COMPARED

Pirtobrutinib
Non-covalent (reversible) BTK inhibitor, given as an oral single agent.

Idelalisib + rituximab
PI3Kδ inhibitor combined with an anti-CD20 monoclonal antibody.

In both cohorts, treatment had to begin within 1 year of the first recorded CLL diagnosis.

METHODS

Data source

TriNetX Global Collaborative Network, a federated network of de-identified EHR data. All 173 healthcare organisations queried responded; 43 providers contributed patients to the pirtobrutinib cohort and 36 to the idelalisib/rituximab cohort.

Study population

Adults ≥ 18 years with B-cell CLL who received pirtobrutinib, or idelalisib plus rituximab, within 1 year on or after the CLL diagnosis.

Outcomes & follow-up

Index date was the first recorded CLL diagnosis; outcomes were counted from 1 day after index with no end date applied. Outcomes were CLL relapse and all-cause mortality. Patients were censored after the last fact in their record.

Statistical analysis

1:1 propensity score matching on demographics and comorbidities. Risk ratios, odds ratios and risk differences were calculated for each outcome. Kaplan–Meier estimates with log-rank testing and Cox models were used for time-to-event analyses; the proportional hazards assumption held for both outcomes (p = 0.598 and p = 0.193).

Patient flow

Adults ≥ 18 y with CLL initiating either regimen within 1 year of diagnosis

↓

Pirtobrutinib
586 identified
577 available for matching

Idelalisib + rituximab
154 identified
151 available for matching

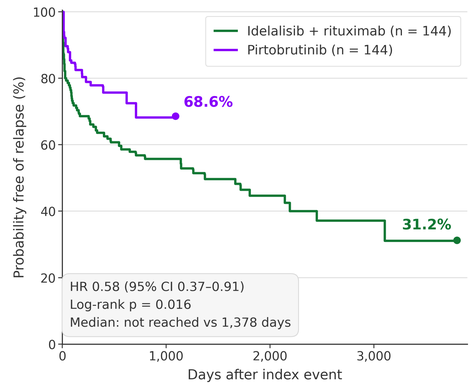
↓ **1:1 propensity score matching on demographics and comorbidities** ↓

Pirtobrutinib
n = 144 matched

Idelalisib + rituximab
n = 144 matched

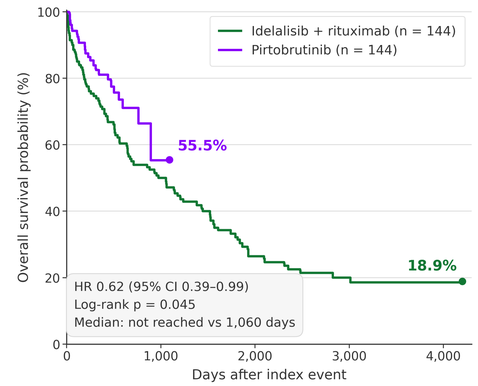
RESULTS

Figure 1. Relapse-free survival



Kaplan–Meier estimates of freedom from CLL relapse in the matched cohorts. Median not reached with pirtobrutinib vs 1,378 days.

Figure 2. Overall survival



Kaplan–Meier estimates of overall survival in the matched cohorts. Median not reached with pirtobrutinib vs 1,060 days.

Figure 3. Proportion of matched patients with each outcome

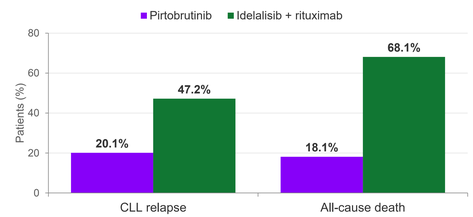


Table 1. Cohort characteristics after matching

Characteristic	Pirtobrutinib (n = 144)	Idelalisib + R (n = 144)	Std. diff.
Age at index, mean ± SD, y	69.9 ± 10.1	70.9 ± 8.8	0.105
Male, n (%)	95 (66.0)	96 (66.7)	0.015
White, n (%)	125 (86.8)	121 (84.0)	0.079
Black or African American, n (%)	13 (9.0)	10 (6.9)	0.077
Hispanic or Latino, n (%)	**0 (0)**	**10 (6.9)**	**0.386**
Hypertension, n (%)	86 (59.7)	89 (61.8)	0.043
Diabetes mellitus, n (%)	30 (20.8)	35 (24.3)	0.083
Chronic kidney disease, n (%)	36 (25.0)	41 (28.5)	0.079
Heart failure, n (%)	25 (17.4)	28 (19.4)	0.054
Coronary artery disease, n (%)	38 (26.4)	35 (24.3)	0.048
COPD, n (%)	19 (13.2)	18 (12.5)	0.021

All standardised differences < 0.11 except Hispanic ethnicity (0.386; p = 0.001); all other p values were 0.37 or higher. Ethnicity was not recorded for 18.7% and 11.2% of the two cohorts.

Table 2. Primary outcomes in the matched cohorts

Outcome	Pirtobrutinib (n = 144)	Idelalisib + rituximab (n = 144)	Effect estimate (95% CI)	p value
CLL RELAPSE				
Patients with relapse, n (%)	29 (20.1)	68 (47.2)	RR 0.43 (0.30–0.62) · OR 0.28 (0.17–0.48) Risk difference −27.1% (−37.5 to −16.6)	< 0.001
Median relapse-free survival (probability at end of follow-up)	Not reached (68.6%)	1,378 days (31.3%)	HR 0.58 (0.37–0.91)	0.016
ALL-CAUSE MORTALITY				
Deaths, n (%)	26 (18.1)	98 (68.1)	RR 0.27 (0.18–0.38) · OR 0.10 (0.06–0.18) Risk difference −50.0% (−59.9 to −40.1)	< 0.001
Median overall survival (probability at end of follow-up)	Not reached (55.5%)	1,060 days (18.9%)	HR 0.62 (0.39–0.99)	0.045

p values for event counts and risk differences are from the risk analysis; p values for median survival are log-rank. TriNetX reports no p value for the risk ratio or odds ratio. RR = risk ratio; OR = odds ratio; HR = hazard ratio.

CONCLUSIONS

In this propensity-matched real-world analysis, pirtobrutinib was associated with significantly lower relapse and all-cause mortality than idelalisib plus rituximab in CLL.

Key findings

- Relapse occurred in 20.1% of pirtobrutinib-treated patients versus 47.2% with idelalisib/rituximab.
- All-cause mortality was 18.1% versus 68.1%.
- Median relapse-free and overall survival were not reached with pirtobrutinib, versus 1,378 and 1,060 days.
- Both time-to-event comparisons favoured pirtobrutinib (RFS HR 0.58; OS HR 0.62).

Limitations

- Retrospective, non-randomised analysis of routinely collected EHR data.
- Given the size of the mortality difference, residual confounding by indication (particularly differential frailty and prior therapy burden) cannot be excluded.
- A Hispanic ethnicity imbalance persisted after matching (0% vs 6.9%).
- The unrestricted diagnosis-date window may introduce survivorship bias: idelalisib/rituximab patients with older index dates may represent a more treatment-refractory historical population.

Take-home message

These findings support pirtobrutinib as an effective option in routine CLL practice and underscore the value of prospective comparative studies.

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