CLL-194

Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison of 3 Randomized Phase 3 Trials

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OBJECTIVE

To evaluate the outcomes of Bruton's tyrosine kinase inhibitor (BTKi) treatment in patients with R/R CLL by comparing the efficacy of ibrutinib in RESONATE to ALPINE and ELEVATE-RR using a MAIC analysis

CONCLUSIONS

In the phase 3 randomized trials in R/R CLL, continuous ibrutinib treatment was associated with robust clinical response

Ibrutinib PFS outcomes were consistent between RESONATE and ELEVATE-RR; however, significant differences in the performance of ibrutinib within ALPINE were identified

Taking into consideration the inherent limitations of indirect comparisons, these results highlight the need for careful consideration of elements of protocol design, center selection, or treatment management that may lead to a significant impact on BTKi performance in clinical studies

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INTRODUCTION

- Ibrutinib is a standard therapy for patients with chronic lymphocytic leukemia (CLL), with demonstrated efficacy in the first-line and relapsed/refractory (R/R) settings
- Within R/R CLL, single-agent ibrutinib was evaluated in 3 randomized phase 3 studies: RESONATE,[1] ALPINE,[2] and ELEVATE-RR (in patients with del[11q] or del[17p] abnormalities)[3]
- Comparative efficacy of ibrutinib in those 3 trials has not yet been assessed

METHODS

Clinical Studies

- All 3 phase 3 trials were randomized (1:1), open-label, and conducted in patients with R/R CLL to compare the efficacy and safety of
  - Ibrutinib and ofatumumab (RESONATE, NCT01578707, N=391)[1]
  - Ibrutinib and zanubrutinib (ALPINE, NCT03734016, N=652)[2]
  - Ibrutinib and acalabrutinib (ELEVATE-RR, NCT02477696, N=533); in this study, patients were also required to have a confirmed del(17p) or del(11q) mutation[3]

Data Analysis

- Individual patient data of ibrutinib-treated patients from RESONATE were separately adjusted to the ibrutinib-treated arms of ALPINE and ELEVATE-RR using the matching-adjusted indirect comparison (MAIC) methodology[4]
- The baseline characteristics used for the MAIC procedure were
  - Age ≥75 years
  - Presence of bulky disease (at least 5 cm)
  - History of ≥3 (ALPINE) or ≥4 prior treatments (ELEVATE-RR)
  - β_2 microglobulin >3.5 mg/L
  - del(11q) mutation
  - del(17p) mutation
- Patient data from RESONATE with missing values for the baseline characteristics listed above were omitted prior to the matching procedure
- For the comparison with ELEVATE-RR, only patients with del(17p) or del(11q) from RESONATE were included
- Once ibrutinib-treated populations were matched, adjusted overall response rate (ORR) and progression-free survival (PFS) from RESONATE were compared with the corresponding published outcomes from ALPINE[2] and ELEVATE-RR[3]
  - For PFS estimates, individual patient data for ALPINE and ELEVATE-RR were extracted from published Kaplan-Meier curves[2,3]
- PFS hazard ratios (HRs) were calculated using a weighted Cox model
- Across all 3 studies, ORR was calculated as CR + CRi + nPR + PR (CR, complete remission; CRi, complete remission with incomplete cell count recovery; nPR, nodular partial remission; PR, partial remission)
  - PR with lymphocytosis and overall response (OR) with lymphocytosis were not included in assessment of ORR

RESULTS

- The analysis comprised 785 ibrutinib-treated patients across RESONATE (n=195), ALPINE (n=325), and ELEVATE-RR (n=265)
- Following the exclusion of patients with missing values and the adjustment procedure, the effective RESONATE sample size was reduced to 95 patients (vs ALPINE) and to 69 patients (vs ELEVATE-RR)

Selected Baseline Characteristics of RESONATE Ibrutinib Arm Before and After Matching to Ibrutinib Arms of ALPINE and ELEVATE-RR

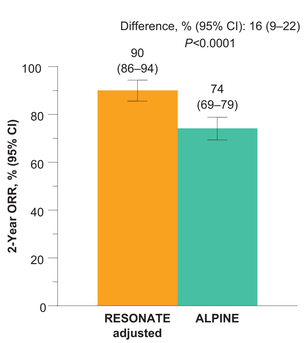
Baseline Characteristic, n (%)	RESONATE[1] (published) n=195	RESONATE Adjusted vs ALPINE			RESONATE Adjusted vs ELEVATE-RR		
		ALPINE n=325	RESONATE unadjusted[a] n=179	RESONATE adjusted ESS=95	ELEVATE-RR n=265	RESONATE unadjusted[a] n=106	RESONATE adjusted ESS=69
Age ≥75 years	22.1	21.2	21.8	21.2	16.2	18.9	16.2
Presence of bulky disease[b]	63.6	45.8	63.7	45.8	51.3	69.8	51.3
History of ≥3 prior treatments	52.8	20.9	52.5	20.9	NA	NA	NA
History of ≥4 prior treatments	52.8	NA	NA	NA	10.6	36.8	10.6
β_2 microglobulin >3.5 mg/L	78.5	66.5	83.8	66.5	80.8	85.8	80.8
del(11q)	32.3	27.2	34.1	27.2	66.0	57.5	66.0
del(17p)	32.3	15.4	31.3	15.4	45.3	52.8	45.3

ESS, effective sample size; NA, not applicable.
[a]In RESONATE unadjusted populations, data from RESONATE participants with missing baseline values used for matching were omitted prior to the matching procedure. [b]At least 5 cm.

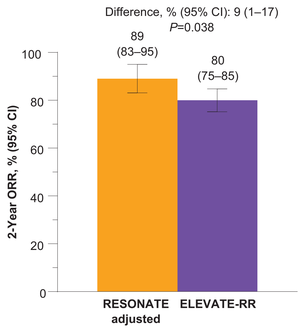
- Median follow-up times were 36.0 months versus 29.6 months (RESONATE adjusted vs ALPINE) and 36.1 months versus 40.9 months (RESONATE adjusted vs ELEVATE-RR)
- In both comparisons, the ORR difference in favor of RESONATE adjusted was statistically significant
- 2-year PFS estimates in RESONATE adjusted were significantly higher than the corresponding values in ALPINE (81% vs 66%, *P*=0.0112); compared with ELEVATE-RR, RESONATE adjusted had a greater 2-year PFS, although this difference was not statistically significant (79% vs 69%, *P*=0.51)

For Ibrutinib-Treated Patients in RESONATE, 2-Year ORR Estimates Were Significantly Higher Than Those in (A) ALPINE and (B) ELEVATE-RR

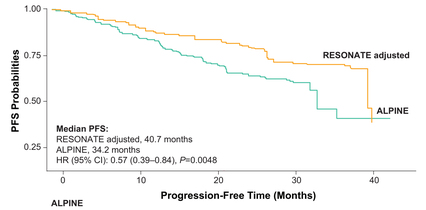
A. RESONATE Adjusted vs ALPINE



B. RESONATE Adjusted vs ELEVATE-RR



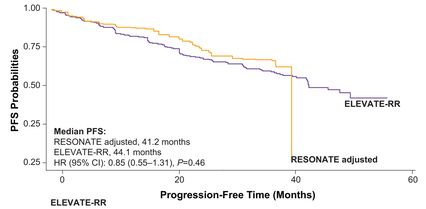
For Ibrutinib-Treated Patients in RESONATE, Median PFS Was Significantly Longer and the 2-Year PFS Estimate Was Higher Versus ALPINE



ALPINE								
Number at Risk	325	292	259	227	128	97	9	1
Cumulative Observed Events	0	22	49	78	101	107	118	119
RESONATE adjusted								
Number at Risk	179	170	158	149	139	119	64	0
Cumulative Observed Events	0	8	18	26	33	49	52	58

Due to variations inherent to manual data collection, there was a discrepancy (<1%) between the numbers of identified and published censoring events. This discrepancy is not likely to affect the conclusions.

For Ibrutinib-Treated Patients in RESONATE, Median PFS Was Longer and the 2-Year PFS Estimate Was Higher Versus ELEVATE-RR, but the Difference Was not Statistically Significant



ELEVATE-RR											
Number at Risk	265	233	204	182	161	151	121	75	32	5	0
Cumulative Observed Events	0	20	41	55	75	84	94	102	111	113	113
RESONATE adjusted											
Number at Risk	106	98	92	88	80	71	40	0	0	0	0
Cumulative Observed Events	0	8	12	15	22	32	34	37	37	37	37

Due to variations inherent to manual data collection, there was a discrepancy (<1%) between the numbers of identified and published censoring events. This discrepancy is not likely to affect the conclusions.

References

1. Byrd JC et al. *N Engl J Med*. 2014;371:213–223.
2. Brown JR et al. *N Engl J Med*. 2023;388:319–332.
3. Byrd JC et al. *J Clin Oncol*. 2021;39:3441–3452.
4. Signorovitch JE et al. *Value Health*. 2021;15:940–947.