# Ibrutinib Efficacy Across Subgroups of Patients With High-Risk Chronic Lymphocytic Leukemia: A Systematic Literature Review



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## INTRODUCTION

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is the most common type of leukemia in the Western hemisphere, representing approximately 11% of all hematologic malignancies[1,2]
- Patients with CLL and high-risk genomic features, including del(17p), *TP53* mutations, del(11q), unmutated immunoglobulin heavy-chain variable (uIGHV), and/or complex karyotype, are more likely to experience adverse outcomes following chemotherapy[3]
- Ibrutinib is a first-in-class, once-daily, covalent Bruton tyrosine kinase (BTK) inhibitor approved globally for the treatment of CLL/SLL, including in patients with del(17p) mutations[4]

## OBJECTIVE

- To assess the efficacy and safety of single-agent ibrutinib in patients with high-risk CLL through a systematic literature review (SLR)
- To report comparisons of progression-free survival (PFS) and overall response rates (ORRs) among patients with CLL with high-risk mutations

## METHODS

### Data source

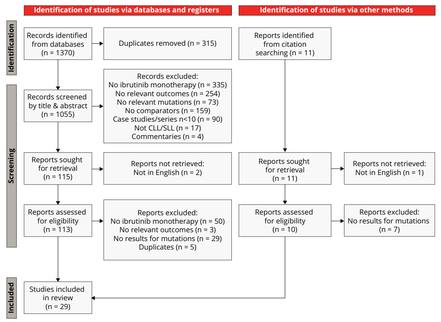
- Using standard SLR methodologies, publications were collected from Embase and PubMed
- Studies were included if they reported on patients diagnosed with CLL who received single-agent ibrutinib and had any of the following high-risk genomic mutations: del(17p)/*TP53*, del(11q), uIGHV, and/or complex karyotype
- Publications reporting any relevant efficacy and safety data were included, with no time or geographic limits on the search

## RESULTS

### Study selection

- A total of 1375 publications were screened, and 29 were included in the SLR (**Figure 1**)

**Figure 1: PRISMA diagram of included studies**



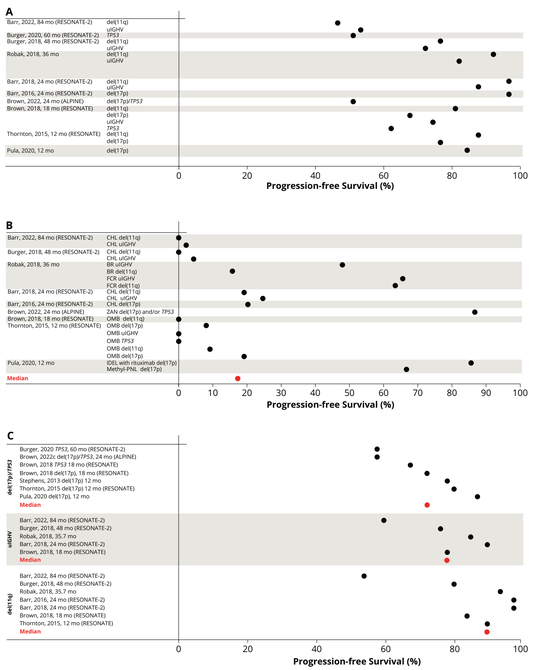

CLL, chronic lymphocytic leukemia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLL, small lymphocytic lymphoma.

- Of the 29 studies identified, total of 6 studies (N = 2111 patients) included subgroup data evaluating the effects of single-agent ibrutinib in patients with del(17p)/*TP53*, uIGHV, and del(11q)/mutated IGHV (mIGHV) with data analyzed here
  - Of these 6 studies, 4 were randomized controlled trials: ALPINE (NCT03734016), RESONATE (NCT01578707), RESONATE-2 (NCT01722487), ELEVATE-RR (NCT02477696)
  - Two cohort studies were also included: Pula et al[5] and Lamanna et al[6]

### Comparison of outcomes measures

- Compared with other treatments (including ofatumumab; fludarabine, cyclophosphamide, and rituximab [FCR]; and chlorambucil), ibrutinib maintained the most consistent efficacy across different high-risk groups (**Figures 2A and 2B**)[5,7-15]
- PFS rates were lower at comparable time points in patients with del(17p)/*TP53* mutations than in patients with uIGHV or del(11q) mutations (overall cross-study median of 80%) and in patients with uIGHV mutations (overall cross-study median of 93.5%) or del(11q) (overall cross-study median of 84.5%) (**Figure 2C**)[6-14,16-25]

**Figure 2: Summary of PFS rates in high-risk patients treated with (A) ibrutinib, (B) comparators, and (C) ibrutinib, organized by genomic mutation[5,7-25]**




Data from ELEVATE-RR were excluded since PFS rates were not included in the analysis.

BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide, and rituximab; IDEL; idelalisib; OMB, ofatumumab; Methyl-PNL, Methylprednisolone; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy-chain variable; ZAN, zanubrutinib.

- Among patients treated with single-agent ibrutinib in RESONATE, median PFS was similar in patients with and without IGHV mutation (48.4 months vs 49.7 months, respectively)[27]
- ORRs were similar at comparable time points in patients with del(17p)/*TP53* mutations (overall cross-study median of 86%) and in patients with uIGHV (93%) or del(11q) (83%)
- Complete response (CR) rates were lowest in patients with del(17p) mutations (12.8% at 12 months),[5] while patients with uIGHV and mIGHV had CR rates of 34% versus 20% at 60 months[5]; however, CR rates were reported in only 3 publications (**Table 1**)[5,9,10]

**Table 1: Three-way risk comparison of ORR and CR in patients treated with ibrutinib**

| Patients with del(17p)/*TP53* | | Patients with uIGHV | | Patients with del(11q) | |
|---|---|---|---|---|---|
| **Rate** | **Follow-up, months** | **Rate** | **Follow-up, months** | **Rate** | **Follow-up, months** |
| **ORR** | | | | | |
| 79.5% del(17p), n = 39[5] | 24.2 (mean); in the ibrutinib arm[5] | 95% (n = 58)[9,a,d] | 88.5 (median)[9,a,d] | 100% (n = 29)[9,a,d] | 88.5 (median)[9,a,d] |
| NA | NA | 95% (n = 58)[10,a,d] | 29 (median)[10,a,d] | 100% (n = 29)[10,a,d] | 29 (median)[10,a,d] |
| 89% del(17p), n = 63[7,b] | 19 (median) | 92% (n = 98) [7,b] | 19 (median)[7,b] | 90% (n = 63)[7,b] | 19 (median)[7,b] |
| 50% (both, n = 38)[29,c] | 15.3 (median)[29,c] | NA | NA | NA | NA |
| 53.8% del(17p), n = NR[28,c] | 15 (median)[28,c] | NA | NA | 69.1% (n = NR)[28,c] | 15 (median)[28,c] |
| 86% del(17p), n = 63[15,b] | NR[15,b] | 86% (n ~132)[15,b] | NR[15,b] | 79% (n ~63)[15,b] | NR[15,b] |
| 97% del(17p) and relapsed, n = 221[6] 90% del(17p) and relapsed, n = 187[6] | NR[6] | NA | NA | NA | NA |
| **CR** | | | | | |
| 12.8% del(17p), n = 39[5] | 24.2 (mean); in the ibrutinib arm[5] | 34% (n = 58)[9,a,d] | 88.5 (median)[9,a,d] | 45% (n = 29)[9,a,d] | 88.5 (median)[9,a,d] |
| NA | NA | 21% (n = 29)[10,a,d] | 29 (median)[10,a,d] | 14% (n = 29)[10,a,d] | 29 (median)[10,a,d] |

[a]RESONATE-2 clinical program. [b]RESONATE clinical program. [c]ALPINE clinical program. [d]Includes direct comparisons between subgroups. The additional cohort study[6] contained only PFS data and is not included in this table.

CR, complete response; NA, not applicable; NR, not reached; ORR, overall response rate; uIGHV, unmutated immunoglobulin heavy chain variable region.

### Outcomes in high-risk treatment-naive versus previously treated patients

- Most identified publications did not stratify outcomes by prior lines of treatment, and no direct comparisons between previously treated and treatment-naive patients were found
- ORR with ibrutinib treatment in treatment-naive patients was 92%, based on 5 RESONATE-2 publications with different follow-up time points, while RESONATE reported an ORR of 90% across all subgroups of refractory/relapsed patients[9,11,16,20,21]
- The CR rate in treatment-naive patients was 34% at 78 months and 11% at 65 months in the RESONATE-2 and RESONATE trials, respectively[7,10,15,17,21,27]
- The overall survival (OS) rate was 95% at 24 months in RESONATE-2 in treatment-naive patients and 74% at 36 months in previously treated patients[7,10,17,19,21,23]
- PFS data were heterogenous, but rates were broadly comparable at similar time points between previously treated and treatment-naive patients

## CONCLUSIONS

- Ibrutinib demonstrates high efficacy across different subgroups of patients with high-risk genomic features, including those with del(17p), *TP53* mutations, or uIGHV
- Outcomes in high-risk patients treated with ibrutinib were better than those in patients treated with non-BTK inhibitors; comparisons of ibrutinib with other BTK inhibitors were limited by methodology

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REFERENCES:

1. van der Straten L et al. *Front Oncol*. 2021;11:780085. 2. Zhou et al. *Onco Targets Ther*. 2020;13:4877-4892. 3. Gruber M et al. *Nature*. 2019;570(7762):474-479. 4. Imbruvica (ibrutinib) [prescribing Information}. South San Francisco, CA: Pharmacyclics LLC; 2024. 5. Pula B et al. *Adv Med Sci*. 2020;65(2):371-377. 6. Lamanna N et al. *Leuk Lymphoma*. 2016;56(suppl 1):147-148. 7. Brown JR et al. *Leukemia*. 2018;32(1):83-91. 8. Brown JR et al. *Blood*. 2022;140(suppl 2):19-23. 9. Barr PM et al. *Blood Adv*. 2022;6(11):3440-3450. 10. Barr PM et al. *Haematologica*. 2018;103(9):1502-1510. 11. Barr P et al. *Blood*. 2016;128(22) 12. Burger JA et al. *Leukemia*. 2020;34(3):787-798. 13. Burger J et al. *HemaSphere*. 2018;2(suppl 2):123-124. 14. Robak T et al. *Am J Hematol*. 2018;93(11):1402-1410. 15. Thornton P et al. *Hematol Oncol*. 2015;33(suppl 1). Abstract 055. 16. Tedeschi A et al. *Hematol Oncol*. 2019;37(suppl 2):103-104. 17. Burger J et al. *Clin Lymphoma Myeloma Leuk*. 2019;19(suppl 1):S274. 18. Robak T et al. *Leuk Lymphoma*. 2021;62(suppl 1):592-593. 19. Alrawashdh N et al. *Clin Lymphoma Myeloma Leuk*. 2021;21(11):e820-e831. 20. Barr PM et al. *J Clin Oncol*. 2021;39(15 suppl):7523. 21. Burger J et al. *Clin Lymphoma Myeloma Leuk*. 2021;21(suppl 1):S316. 22. Barr PM et al. *J Clin Oncol*. 2019;37(suppl 15):7510. 23. Hillmen P et al. *Leuk Lymphoma*. 2021;62(suppl 1):S54-S55. 24. Byrd JC et al. *J Clin Oncol*. 2021;39(31):3441-3452. 25. Sultan A et al. *Blood*. 2019;134(suppl 1):5481. 26. Stephens DM et al. *Blood*. 2013;122(21):2872. 27. Munir T et al. *Am J of Hematol*. 2019;94(12):1353-1363. 28. Hillmen P et al. *Br J Haematol*. 2022;197(suppl 1):92-93. 29. Hillmen P et al. *J Clin Oncol*. 2023;41(5):1035-1045.

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