Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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OBJECTIVE

To report final long-term efficacy and safety analyses of first-line (1L) ibrutinib treatment with up to 10-years of follow-up from the RESONATE-2 trial (NCT01722487)

CONCLUSIONS

The RESONATE-2 landmark study supported the first global approval of a Bruton tyrosine kinase inhibitor (BTKi) for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). This final analysis, with up to 10 years of follow-up, provides the longest follow-up among BTKis in the 1L setting, demonstrating a median progression-free survival for ibrutinib of 8.9 years and median overall survival that was not estimable

Responses deepened over time, supporting durability of response in patients receiving long-term ibrutinib. At study closure, 27% of patients remained on 1L ibrutinib

No new safety signals for ibrutinib were observed during this long-term follow-up, and most adverse events were effectively managed with dose modifications

1L single-agent ibrutinib continues to demonstrate significant and durable clinical benefit in older adults with CLL/SLL, including those with high-risk genomic and clinical features

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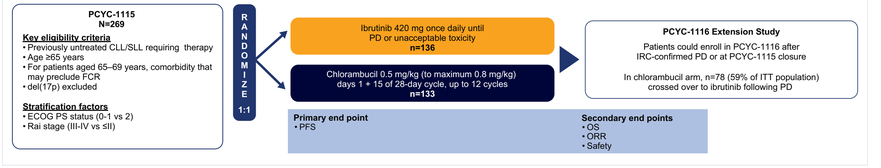
INTRODUCTION

- RESONATE-2 (PCYC-1115/PCYC-1116, NCT01722487/NCT01724346) was an international phase 3 study evaluating first-line (1L) ibrutinib or chlorambucil in patients aged ≥65 years with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1]
- Ibrutinib, a once-daily Bruton tyrosine kinase inhibitor (BTKi), is approved globally, including in Europe and the United States, for the treatment of CLL/SLL in both 1L and relapsed/refractory settings[2,3]
- Ibrutinib is the only targeted therapy to demonstrate both a significant progression-free survival (PFS)[4–7] and overall survival (OS)[4,5,8] benefit over chemotherapy or chemoimmunotherapy in multiple randomized phase 3 studies in 1L CLL/SLL
- The landmark RESONATE-2 study provides the longest follow-up among BTKis in the 1L setting
- Given the observed PFS and OS, evaluating long-term efficacy and safety of ibrutinib treatment is critical to inform clinical practice

METHODS

- Details of the study, including inclusion and exclusion criteria, have been previously described[1]
- End points included PFS, OS, overall response rate (ORR), improvement in hematologic parameters, and safety
  - PFS and OS were analyzed according to the Kaplan-Meier method
  - Long-term response was investigator-assessed per International Workshop on CLL 2008 criteria
  - Hazard ratios (HRs) were estimated using a stratified Cox regression model

Study Design of RESONATE-2

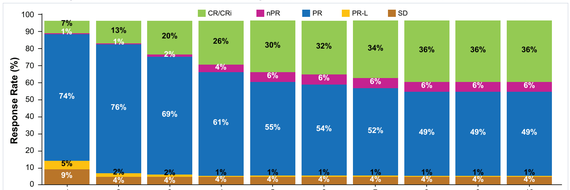


ECOG PS, Eastern Cooperative Oncology Group Performance Status; FCR, fludarabine, cyclophosphamide, and rituximab; IRC, independent review committee; ITT, intent to treat; PD, progressive disease.

RESULTS

- Baseline clinical and genomic characteristics were well balanced between the arms in RESONATE-2 (**Supplementary Table 1**)
- Among patients in the ibrutinib and chlorambucil arms, respectively, 29 of 130 patients with testing results (22%) and 25 of 121 patients (21%) had del(11q) mutation, 58 of 101 patients (57%) and 60 of 103 patients (58%) had unmutated immunoglobulin IGHV, 12 of 124 patients (10%) and 3 of 94 patients (3%) had *TP53* mutation, and 6 of 93 patients (7%) and 8 of 90 patients (9%) had complex karyotype

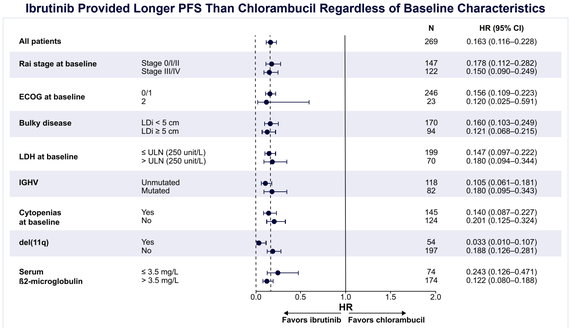
The Proportion of Patients With Best Response of CR/CRi Was Stable After the First 7 Years



CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

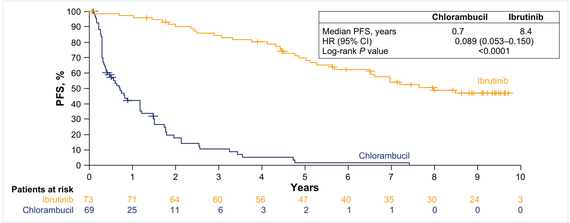
- Best CR and ORR (including PR-L) increased to 36% and 92%, respectively, until 8 years, and remained stable thereafter

Ibrutinib Provided Longer PFS Than Chlorambucil Regardless of Baseline Characteristics

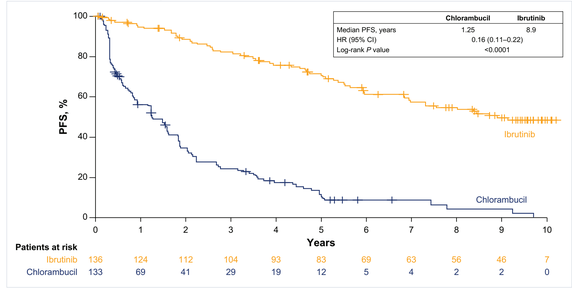


LDH, lactate dehydrogenase; LDi, longest transverse diameter of a lesion; ULN, upper limit normal.

In Patients With ≥1 High Prognostic Risk Factors Including Mutated *TP53*/Unmutated IGHV/del(11q), PFS Was Significantly Longer for Patients Treated With Ibrutinib Versus Chlorambucil

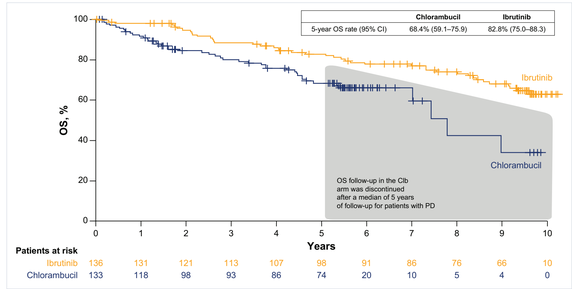


At Final Analysis, Median PFS With Ibrutinib Was Reached at 8.9 Years



- At 9 years, the PFS rates were 49.7% (95% CI, 40.2–58.4) in the ibrutinib arm and 4.4% (95% CI, 1.1–11.5) in the chlorambucil arm

OS Benefit Was Sustained for Patients Receiving Ibrutinib



Cb, chlorambucil.

- At 9 years, the OS rate was 68.0% (95% CI, 58.6–75.7) in the ibrutinib arm
- At this final analysis the median OS was not estimable in the ibrutinib arm
- In patients with ≥1 high prognostic risk factors including mutated *TP53*/unmutated IGHV/del(11q), OS was significantly longer for patients treated with ibrutinib versus chlorambucil (**Supplementary Figure 1**)

After up to 10 Years of Follow-Up, 27% of Patients Initially Randomly Assigned to Ibrutinib Remained on Ibrutinib Treatment

	Ibrutinib N=135
Median (range) duration of ibrutinib treatment, years	6.2 (0.06–10.2)
Continuing ibrutinib at study closure, n (%)	37 (27)
Discontinued ibrutinib, n (%)	
Due to AE	44 (33)
Due to PD	18 (13)

AE, adverse event.

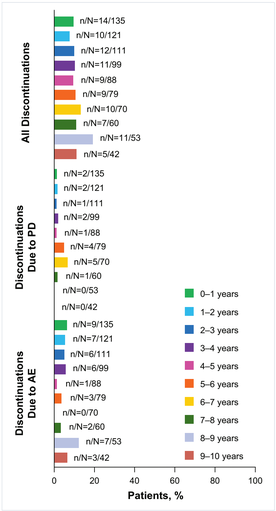
- After discontinuation of 1L ibrutinib, 24 patients (18%) received subsequent antineoplastic therapies (**Supplementary Table 2**)
- Safety and tolerability were consistent with previous follow-up (**Supplementary Table 3**)
- COVID-19 disease occurred in 24 patients (18%)
  - Grade 3–5 COVID-19 in 8 patients
- Dose reductions due to AEs generally decreased over time (**Supplementary Figure 2**)
- Of 34 patients who had AEs of any grade leading to dose reduction, 28 patients (82%) had all AEs resolved

Baseline Clinical and Genomic Characteristics of Patients Remaining on Ibrutinib at Study Closure and of Patients Who Discontinued Were Largely Similar

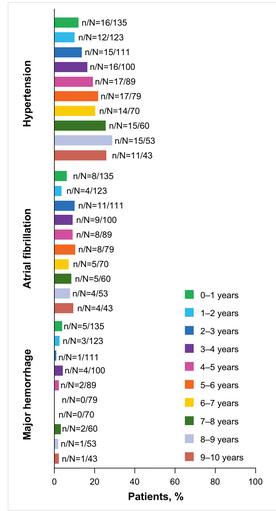
	On Ibrutinib N=37	Discontinued Ibrutinib N=98
Age, median (range), years	71 (65–82)	73 (65–89)
Men, n (%)	16 (43)	72 (74)
ECOG PS, n (%)		
0	19 (51)	41 (42)
1–2	18 (49)	57 (58)
Rai stage III or IV, n (%)	18 (49)	42 (43)
CIRS score >6, n (%)	10 (27)	32 (33)
Creatinine clearance <60 mL/min, n (%)	15 (41)	45 (46)
Bulky disease ≥5 cm, n (%)	11 (30)	43 (44)
β2-macroglobulin >3.5 mg/L, n (%)	23 (62)	62 (63)
Hemoglobin ≤11 g/dL, n (%)	14 (38)	37 (38)
Platelet count ≤100 x 10^9 /L, n (%)	12 (32)	23 (24)
High prognostic risk features,[a] n (%)	19 (51)	54 (55)
del(11q), n/N (%)	5/35 (14)	24/94 (26)
Unmutated IGHV, n/N (%)	17/32 (53)	41/89 (46)
TP53 mutation, n/N (%)	2/36 (6)	9/94 (10)
Complex karyotype, n/N (%)	1/24 (4)	5/68 (7)
NOTCH1 mutation, n/N (%)	8/36 (22)	23/88 (26)

[a]del(11q), unmutated IGHV, and/or *TP53* mutation.
CIRS, Cumulative Illness Rating Scale; *NOTCH1*, neurogenic locus notch homolog protein 1.

No Increasing Trend in Discontinuations Was Observed Over Time



Prevalence of Most AEs of Interest Decreased Over Time



References

1. Burger JA et al. *N Engl J Med.* 2015;373(25):2425-2437.
2. IMBRUVICA [package insert]. South San Francisco, CA: Pharmacyclics LLC; 2024.
3. European Medicines Agency. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf. Accessed May 13, 2024.
4. Burger JA et al. *Leukemia.* 2020;34(3):787-798.
5. Salles G et al. *Ann Hematol.* 2019;98(12):2749-2760.
6. Moreno C et al. *Lancet Oncol.* 2019;20(1):43-56.
7. Woyach JA et al. *N Eng J Med.* 2018;379(26):2517-2528.
8. Shanafelt TD et al. *N Engl J Med.* 2019;381(5):432-443.