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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

https://www.congresshub.com/Oncology/EHA2024/Ibrutinib/Burger

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AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. No honoraria or payments were made for authorship. Medical writing support was provided by Agnieszka Looney, PhD, and was funded by AbbVie.

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Presented at the European Hematology Association (EHA) Hybrid Congress; June 13–16, 2024; Madrid, Spain

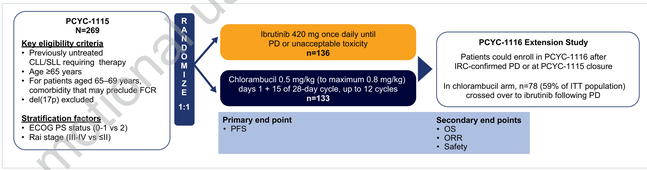
INTRODUCTION

- 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

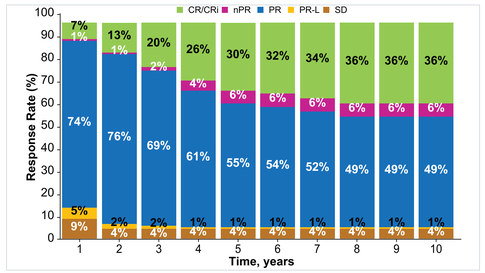


ECOG PS, Eastern Cooperative Oncology Group Performance Status; FCR, fludarabine, cyclophosphamide, and rituximab; IRC, independent review committee; ITT, intent to treat; PD, progressive disease.

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

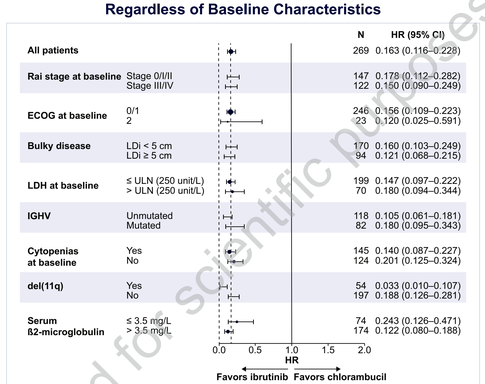
The Proportion of Patients With Best Response of CR/CRi Was Stable After the First 7 Years



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.

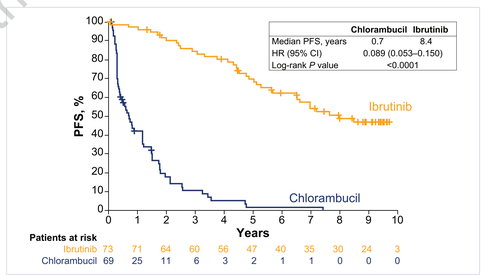
- Best CR and ORR (including PR-L) increased to 36% and 92%, respectively, until 8 years, and remained stable thereafter

Ibrutinib Provided Longer PFS Than Chlorambucil Regardless of Baseline Characteristics

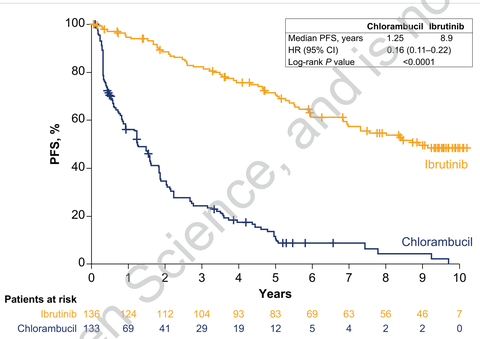


LDH, lactate dehydrogenase; LDi, longest transverse diameter of a lesion; ULN, upper limit normal.

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

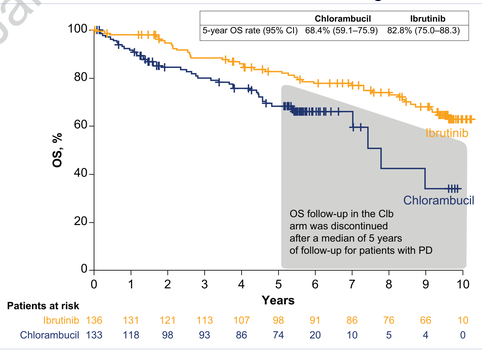


At Final Analysis, Median PFS With Ibrutinib Was Reached at 8.9 Years



- 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



Clb, 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.

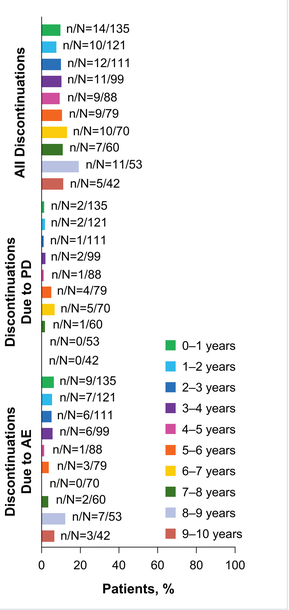
- After discontinuation of 1L ibrutinib, 24 patients (18%) received subsequent antineoplastic therapies (**Supplementary Table 2**)
- Safety and tolerability were consistent with previous follow-up (**Supplementary Table 3**)
- COVID-19 disease occurred in 24 patients (18%)
  - Grade 3–5 COVID-19 in 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

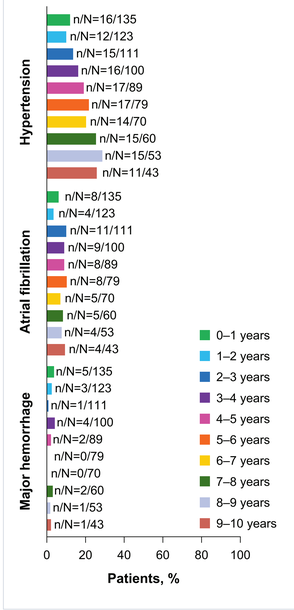
	On Ibrutinib N=37	Discontinued Ibrutinib N=98
Age, median (range), years	71 (65–82)	73 (65–89)
Men, n (%)	16 (43)	72 (74)
ECOG PS, n (%)		
0	19 (51)	41 (42)
1–2	18 (49)	57 (58)
Rai stage III or IV, n (%)	18 (49)	42 (43)
CIRS score >6, n (%)	10 (27)	32 (33)
Creatinine clearance <60 mL/min, n (%)	15 (41)	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



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