Ibrutinib Therapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Up to 7 Years of Follow-Up From the RESONATE-2 Study

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INTRODUCTION

- Ibrutinib, a once-daily Bruton's tyrosine kinase (BTK) inhibitor, is approved in the US for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).[1]
  - Ibrutinib is the only therapy for CLL/SLL to demonstrate both a significant progression-free survival (PFS)[2,7] and overall survival (OS)[2,3,6,7] benefit in multiple randomized phase 3 studies for patients with first-line or relapsed/refractory CLL/SLL.
  - Real-world ibrutinib data in CLL are generally consistent with clinical trial results.[8-20]
- At last update, median PFS for ibrutinib was not reached; 70% of patients with CLL treated with first-line ibrutinib remain progression-free and alive.[21]
- Given the durable efficacy observed with single-agent ibrutinib treatment, ongoing evaluations of long-term efficacy and safety are critical to inform clinical decision-making.

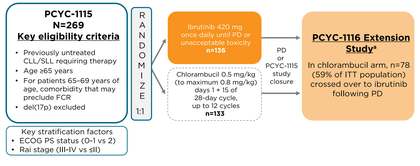
OBJECTIVE

- To describe the long-term efficacy and safety with up to 7 years of follow-up from RESONATE-2, the first randomized phase 3 study to establish efficacy of first-line ibrutinib treatment in CLL/SLL

METHODS

- RESONATE-2 is a phase 3, open-label, multicenter, international, randomized study (PCYC-1115/1116; NCT01722487) in first-line CLL/SLL (**Figure 1**).[2,21]
- Long-term efficacy (PFS, overall response rate [ORR]) is reported per the investigator.
  - After a median follow-up of 5 years, the protocol was amended to provide up to 10 years of PFS follow-up for both arms, and up to 10 years of OS follow-up for the ibrutinib arm only.
- Safety data are reported for ongoing ibrutinib treatment arm only.

Figure 1. RESONATE-2 Study Schema



*Patients could enroll in separate extension study PCYC-1116 after IRC-confirmed PD or at study PCYC-1115 closure for continuing treatment and follow-up.
ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine + cyclophosphamide + rituximab; IRC, independent review committee; ITT, intention-to treat. PD, disease progression.

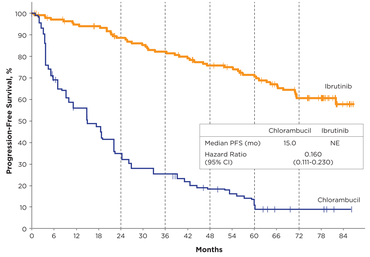
RESULTS

- Baseline patient characteristics were well-matched and the majority of patients were aged 70 years or older (median 73 years), 35% had bulky disease, 39% had anemia (Hb <11 g/dL), and 65% had β_2-microglobulin (B2M) >3.5 mg/L.
- 22% (54/251) of evaluable patients had del(11q), 58% (118/204) had unmutated IGHV.
- 53% (142/269) of all patients in the ITT population had one or more high-risk features (*TP53* mutation, del[11q], and/or unmutated IGHV).

RESULTS (CONT.)

Efficacy

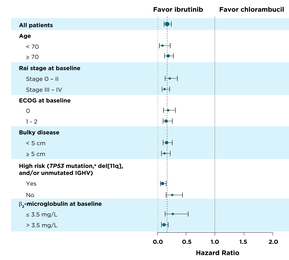
Figure 2. PFS: Ibrutinib vs Chlorambucil



HR, hazard ratio.
HR from stratified Cox regression model.

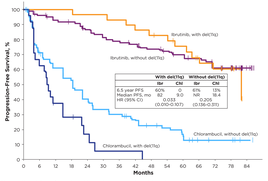
- With up to 7 years of follow-up, the median PFS was not reached for the ibrutinib arm (**Figure 2**).
  - Ibrutinib-treated patients had an 84% reduction in risk of progression or death.
- At 6.5 years, 61% vs 9% of ibrutinib vs chlorambucil patients were estimated to be progression free and alive.
  - Only 12% of patients randomized to ibrutinib progressed while on active ibrutinib treatment.
- Superior benefit for ibrutinib vs chlorambucil was maintained across subgroup analysis factors, including high-risk genomic features and other baseline clinical characteristics such as advanced stage and bulky disease (**Figure 3**).

Figure 3. PFS in Patient Subgroups of Interest



TP53 mutation per arm: ibrutinib (n=11) and chlorambucil (n=3).
HR from stratified Cox regression model.

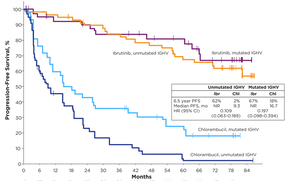
Figure 4. PFS by del(11q) Status



HR from stratified Cox regression model; artifact at the end of the curve for ibrutinib patients with del(11q) is due to the extremely low patient numbers at these time points.

- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil (**Figure 4**).
- At 6.5 years, PFS rates for ibrutinib vs chlorambucil for patients with del(11q) were 60% vs 0%, and without del(11q) were 61% vs 13%.
- PFS was similar in ibrutinib-treated patients with and without del(11q).

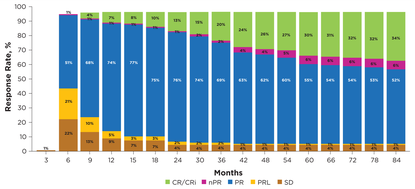
Figure 5. PFS by IGHV Status



HR from stratified Cox regression model.

- Ibrutinib led to 89% and 80% reductions in the risk of PD or death in patients with unmutated and mutated IGHV, respectively, vs chlorambucil (**Figure 5**).
- At 6.5 years, PFS rates for ibrutinib vs chlorambucil for patients with unmutated IGHV were 62% vs 2%, and with mutated IGHV were 67% vs 18%.
- PFS was similar in ibrutinib-treated patients with unmutated and mutated IGHV.

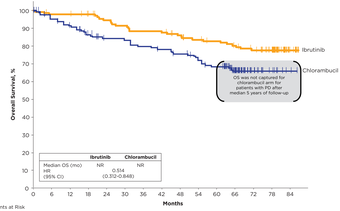
Figure 6. Investigator-Assessed Overall Response Rate With Ibrutinib



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.

- At up to 7 years of follow-up, the CR/CRi rate increased over time to 34% (ORR 92%) (**Figure 6**).
  - Median duration of response (range, <0.1 to 83) and complete response (range, <0.1 to 79 months) were not reached.
- For ibrutinib-treated patients, ORR and CR rates were similar, irrespective of del(11q) or IGHV mutation status.

Figure 7. Ibrutinib OS



HR from stratified Cox regression model.

- Patients treated with ibrutinib had improved OS and a 49% reduction in death (**Figure 7**).
- 78% of ibrutinib-treated patients were estimated to be alive at 6.5 years.
  - OS estimates at 5 years for ibrutinib vs chlorambucil were 83% vs 68%.
- Patients with high-risk genomic features (*TP53* mutation, del[11q], or unmutated IGHV) had similar improved OS with ibrutinib treatment as observed for all patients (HR: 0.489 [95% CI, 0.249–0.960]).

Safety

Table 1. Ibrutinib Treatment Disposition

	First-Line Ibrutinib (n=136*)
Median duration of ibrutinib treatment, years[a] (range)	6.2 (0.06–7.2)
Continuing ibrutinib on study, n (%)	64 (47)
Discontinued ibrutinib, n (%)	
AE	31 (23)
PD	16 (12)
Death	11 (8)
Withdrawal by patient	9 (7)
Investigator decision	4 (3)

*One patient received no doses of ibrutinib; *74.0 months (0.7–86.8).
AE, adverse event.

- More than half of patients continued to receive single-agent ibrutinib for at least 6 years.
- 47% of patients continue first-line ibrutinib treatment on study with this follow-up (**Table 1**).

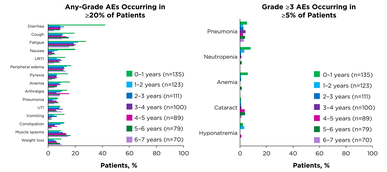
Table 2. Concomitant Medications of Clinical Interest

	Ibrutinib n=135	Chlorambucil n=132
Antithrombotics, n (%)		
Antiplatelets	96 (71)	71 (54)
Anticoagulants	80 (59)	67 (51)
Antihypertensives,* n (%)	48 (36)	13 (10)
Acid related disorders, n (%)	97 (72)	80 (61)
H_2-receptor antagonists	88 (65)	55 (42)
Proton pump inhibitors	23 (17)	10 (8)
Other[b]	75 (56)	47 (36)
Neutrophil Growth Factors, n (%)	5 (4)	1 (1)
	13 (10)	16 (12)

Including antihypertensives, agents acting on the renin-angiotensin system, beta blocking agents, calcium channel blockers. Excluding proton pump inhibitors or H_2-blocker.

- **Table 2** shows concomitant medications of clinical interest by treatment arm.
- Over half of patients on study received concomitant medication for acid-related disorders (54%), including 46% who received proton pump inhibitors.

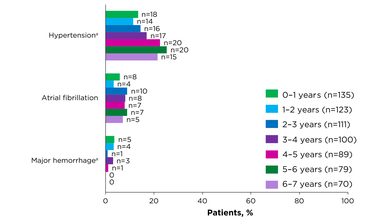
Figure 8. Prevalence[a] of Most Frequent AEs Over Time in Ibrutinib-Treated Patients



Prevalence was determined by the proportion of patients with a given AE (existing event or new onset of an event) during each yearly interval. Multiple onsets of the same AE term within a specific yearly interval were counted once, and the same AE term continuing across several yearly intervals was counted in each of the intervals.
Atrial fibrillation and hypertension are shown in Figure 9, AEs of clinical interest.

- The most frequent any-grade and grade ≥3 AEs are shown (**Figure 8**).

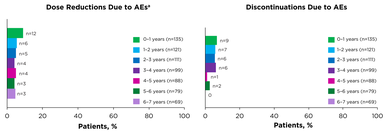
Figure 9. AEs of Clinical Interest Over Time in Patients Treated With Ibrutinib



Combined terms.

- Prevalence rates of any-grade AEs of clinical interest are shown (**Figure 9**).

Figure 10. AEs Leading to Ibrutinib Dose Reductions or Discontinuations



The same patient may appear in more than one year.

- Ibrutinib dose reductions and discontinuations due to AEs are shown over time (**Figure 10**).
- 66/79 patients (84%) had an AE that had a complete resolution following a dose hold of at least 7 days.
- 31 patients (23%) experienced AEs leading to dose reductions.
  - AEs occurring in >1 patient were thrombocytopenia (n=3), and anemia, arthralgia, diarrhea, fatigue, and palpitations (n=2, each).
  - 22/31 (71%) had subsequent AE improvement or resolution.
- At current follow-up (up to 7 years), 31 patients (23%) experienced AEs as the primary cause of ibrutinib discontinuation.
  - AEs occurring in >1 patient were atrial fibrillation (n=5), pneumonia (n=3), and palpitations (n=2).

Table 3. Outcomes Following Ibrutinib Discontinuation

	Discontinued Due to AEs n=31	Discontinued Due to PD n=16	Discontinued Due to Any Cause Other Than Death n=60
Median (range) time on study after discontinuation, months	35.6 (0.2–81.5)	18.7 (<0.1– 53.9)	21.5 (<0.1–81.5)
Median (95% CI) OS after discontinuation, months	NR (15.7–NE)	NR (1–NE)	NR (26.3–NE)
Alive,* n (%)	21 (68)	11 (69)	43 (72)

Includes patients who exited study with no known death.

- First subsequent therapies reported after ibrutinib discontinuation (n=19) included chemoimmunotherapy (n=9; FCR, BR, GC, or vincristine+R), chemotherapy (n=2), novel agents (n=7; including 4 patients on venetoclax), and radiation (n=1).
  - An additional three patients received venetoclax or venetoclax+R as their second subsequent or later line of therapy after ibrutinib.
- Best overall response to the first subsequent drug therapy was reported for 10/18 patients to date: 7/10 responded, 1/10 had stable disease, and 2/10 had PD.

CONCLUSIONS

- In the longest follow-up to date (up to 7 years) from a phase 3 study of first-line BTK-directed therapy, single-agent ibrutinib conferred sustained PFS and OS benefit vs chlorambucil.
  - With ibrutinib treatment, median investigator-assessed PFS and OS were not reached and 6.5-year estimates were 61% and 78%, respectively.
  - Only 16 (12%) patients progressed while receiving ibrutinib.
  - PFS benefit for ibrutinib vs chlorambucil was similar in patients with high-risk genomic features (*TP53* mutation, del[11q], and/or unmutated IGHV) and in lower-risk patients.
    - With up to 7 years of follow-up, ibrutinib benefit was similar for patients with mutated or unmutated IGHV.
  - Responses continued to deepen over time, with further increase in CR/CRi rates with ibrutinib treatment.
- Ibrutinib remains well tolerated with no new safety signals observed with long-term follow-up.
  - Active dose management (dose holds and reductions) to address AEs enabled most patients who required dose management to continue benefiting from ibrutinib treatment.
  - With extended follow-up, rates of discontinuations due to AEs remain low.
- Nearly half of patients remain on ibrutinib at up to 7 years of follow-up.

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DISCLOSURES

PHB: Honoraria and/or travel expenses from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Genentech, Gilead, Janssen, MEI Pharma, Merck, Morphosys, MS Pharma, Pharmacyclics LLC, an AbbVie Company, Seattle Genetics, and TG Therapeutics; research funding from AstraZeneca and TG Therapeutics; **CO:** honoraria from AbbVie, AstraZeneca, Gilead, Incyte, Janssen, Merck, Roche, and Teva; **TR:** honoraria from AstraZeneca and Janssen; consultancy/advisory role with and research funding from Acerta, AstraZeneca, and Janssen; **AT:** honoraria from and speakers bureau for AbbVie, AstraZeneca, BeiGene, and Janssen; **OB:** consultancy/advisory role with AbbVie, AstraZeneca, and Janssen; research funding from Janssen; **JAB:** honoraria from and consulting/advisory role with Janssen; research funding from AstraZeneca, BeiGene, and Pharmacyclics LLC, an AbbVie Company; speakers' bureau for and travel expenses from Gilead, Janssen, Novartis, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; **PH:** consultancy/advisory role with AbbVie, AstraZeneca, and Janssen; research funding from AbbVie, AstraZeneca, Gilead, Janssen, Novartis/GSK, Pharmacyclics LLC, an AbbVie Company, and Roche; speakers' bureau for AbbVie, AstraZeneca, Janssen, and Roche; travel expenses from AbbVie and Janssen; **SEC:** honoraria from AbbVie, Janssen, and Pharmacyclics LLC, an AbbVie Company; consultancy/advisory role with AbbVie, Adaptive, AstraZeneca, BeiGene, Celgene, Genentech, Janssen, Novartis, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, AstraZeneca, and Pharmacyclics LLC, an AbbVie Company; expert testimony for Janssen; travel expenses for consulting and research activities from AbbVie, Janssen, and Pharmacyclics LLC, an AbbVie Company; **SD:** honoraria from AbbVie, AstraZeneca, Janssen, and Pharmacyclics LLC, an AbbVie Company; consultancy/advisory role with AbbVie, AstraZeneca, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, AstraZeneca, and Pharmacyclics LLC, an AbbVie Company; travel expenses from AbbVie, AstraZeneca, and Pharmacyclics LLC, an AbbVie Company; **SG:** honoraria from AbbVie, Celgene, Janssen, Pharmacyclics LLC, an AbbVie Company, and Roche; consultancy/advisory role with AbbVie, Celgene, DAVA Oncology, Genentech Roche, Gilead, Janssen, and Pharmacyclics LLC, an AbbVie Company; research funding from Celgene, Crim, MD Anderson Cancer Center, Oncternal Therapeutics, Pharmacyclics LLC, an AbbVie Company, and Velos; speakers' bureau for AbbVie, DAVA Oncology, Genentech, Gilead, Janssen, Pharmacyclics LLC, an AbbVie Company, and Verastem; patents, royalties, or other intellectual property with the University of California and Oncternal Therapeutics, Inc.; in the development and honing of Cerdulatinib, travel expenses from AbbVie, Bionest Partners, Celgene, DAVA Oncology, Genentech, Gilead, Indy Hematology Review, Janssen, OncLive, Pharmacyclics LLC, an AbbVie Company, Roche, TG Therapeutics, and Verastem; **PG:** honoraria from AbbVie, Acerta/AstraZeneca, Adaptive, Arcule/MGI, BeiGene, Celgene/Juno Therapeutics/Bristol Myers Squibb, Gilead, Janssen, Lilly/Loxo, and Roche; consultancy/advisory role with AbbVie, Acerta/AstraZeneca, Adaptive, Arcule/MGI, BeiGene, Celgene/Juno Therapeutics/Bristol Myers Squibb, Gilead, Janssen, Lilly/Loxo, and Roche; research funding from AbbVie, AstraZeneca, Gilead, Janssen, Novartis, and Sunesis.

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