Abstract: P670

Title: 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

Abstract Type: Poster Presentation

Topic: Chronic lymphocytic leukemia and related disorders - Clinical

Background:

Ibrutinib (Ibr), the first-in-class Bruton's tyrosine kinase inhibitor, demonstrated superior first-line efficacy over chemotherapy/chemoimmunotherapy for the treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in multiple phase 3 trials. With up to 10 years of follow-up, RESONATE-2 provides the longest-term outcomes and safety data of any targeted agent for treatment of CLL/SLL.

Aims:

To report final efficacy and safety analyses of RESONATE-2 (NCT01722487).

Methods:

In this phase 3 study of older adults (≥65 years) with previously untreated CLL/SLL without del(17p), patients (pts) were randomly assigned 1:1 to receive either single-agent Ibr (n=136) or chlorambucil (Clb) (n=133). Ibr was administered orally (420 mg/day) until disease progression or unacceptable toxicity; Clb (0.5–0.8 mg/kg) was administered on days 1 and 15 in a 28-day cycle for up to 12 cycles. Pts could crossover from Clb to Ibr following disease progression. Outcomes included progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and safety. Responses were evaluated per iwCLL 2008 criteria.

Results:

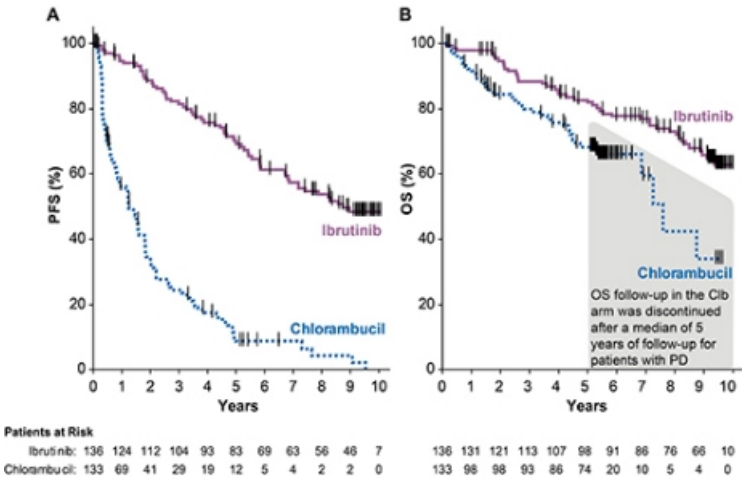
At final analysis, representing up to 10 years of follow-up (median 9.6 years for the Ibr arm and 5.6 years for the Clb arm), pts treated with Ibr demonstrated a significant and sustained PFS benefit versus pts treated with Clb. Median PFS was 8.9 years (95% CI, 7.0–NE) in the Ibr arm versus 1.3 years (95% CI, 0.9–1.6) in the Clb arm (hazard ratio [HR], 0.16; 95% CI, 0.11–0.22; $P<0.0001$) (Figure). PFS was significantly longer for pts treated with Ibr regardless of age, sex, race, Rai stage, Eastern Cooperative Oncology Group performance status, or high-risk mutational status (mutated *TP53*/unmutated IGHV/del[11q]; HR, 0.09; 95% CI, 0.05–0.15; $P<0.0001$). At 9 years, the PFS rate was 49.7% (95% CI, 40.2–58.4) in the Ibr arm and 4.4% (95% CI, 1.1–11.5) in the Clb arm. Median OS with Ibr was not estimable and the 9-year OS rate was 68% (Figure). Among pts treated with Ibr, ORR and complete response (CR/CRi) rates remained unchanged with this follow-up: 91% and 36%, respectively. Rates of adverse events (AEs) of interest in the Ibr arm during years 8–9 and 9–10 were 28% (n=15) and 26% (n=11), respectively for hypertension, and 8% (n=4) and 9% (n=4), respectively for atrial fibrillation. During the entire study period, 34/136 pts (25%) receiving Ibr had AEs of any grade leading to dose reduction, and 28/34 pts (82%) had all AEs resolved. AEs of any grade led to discontinuation of Ibr in 33% of pts (n=44) over the whole study duration, in 13% of pts (n=7) in year 8–9, and in 7% of pts (n=3) in year 9–10. No pts discontinued Ibr due to progressive disease in years 8–10. At study completion, 27% of pts (n/N=37/136) remained on first-line Ibr treatment, with a median duration of treatment of 6.2 years (range, 0.06–10.2).

Summary/Conclusion:

With the longest follow-up to date from a phase 3 study of any targeted therapy for CLL/SLL, this final analysis of the landmark RESONATE-2 study defines median PFS and demonstrates continued OS benefit of single-agent Ibr treatment for pts with previously untreated disease, including those with high-risk genomic features. Median PFS was significantly longer with Ibr versus Clb, and responses to Ibr were sustained over time. At study completion, 27% of pts remained on Ibr, AE rates were stable, and no new safety signals emerged since

the prior report. Sustained efficacy and tolerability of first-line Ibr treatment reinforces the favorable benefit-risk profile.

Figure. Investigator-Assessed Progression-Free Survival (A) and Overall Survival (B)



Keywords: Chlorambucil, B cell chronic lymphocytic leukemia, Clinical trial, ibrutinib