Five-Year Follow-Up After Ibrutinib Therapy for First-Line Treatment of Chronic Lymphocytic Leukemia

Jan Burger,1, 7 Alessandra Tedeschi,2 Paul M. Barr,3 Tadeusz Robak,4 Carolyn Owen,5 Paolo Ghia,6 Osnat Bairey,7 Peter Hillmen,8 Steven E. Coutre,9 Stephen Devereux,10 Sebastian Grosicki,11 Helen McCarthy,12 Jianyong Li,13 David Simpson,14 Fritz Offner,15 Carol Moreno,16 Sandra Dai,17 Indu Lal,17 James P. Dean,17 Thomas J. Kipps18

1Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas, United States; 2Assistance Publique-Hôpitaux de Paris, Hôpital de la Salpêtrière, Paris, France; 3Department of Hematology, University Medical Center Utrecht, Utrecht, the Netherlands; 4Department of Oncology, University of Lucerne, Lucerne, Switzerland; 5Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands; 6University of Szczecin, Szczecin, Poland; 7Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas, United States; 8Karolinska University Hospital, Stockholm, Sweden; 9Stanford University School of Medicine, Stanford, California, United States; 10Institute of Hemaatology, University of Medicine and Pharmacy, Cluj-Napoca, Romania; 11Department of Hematology, Medical University of Lodz, Lodz, Poland; 12Tom Baker Cancer Centre, University of Calgary, Calgary, Canada; 13University Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; 14Leeds Teaching Hospitals, St. James Institute of Oncology, Leeds, United Kingdom; 15Rabin Medical Center, Petah Tikva, Israel; 16The Leeds Teaching Hospitals, St. James Institute of Oncology, Leeds, United Kingdom; 17 Stanford Cancer Center, Stanford University, Stanford, California, United States; 18Institute of Hematology Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel; 19Institute of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; 20Tom Baker Cancer Centre, University of Calgary, Calgary, Canada; 21School of Public Health, Silesian Medical University, Katowice, Poland; 22Royal Bournemouth General Hospital, Bournemouth, United Kingdom; 23Jiangsu Province Hospital, Nanjing, China; 24North Shore Hospital, Auckland, New Zealand; 25University of Antwerp, Gent, Belgium; 26Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; 27Pharmacyclics LLC, an AbbVie Company, Sunnyvale, California, United States; 28UCSD Moores Cancer Center, San Diego, California, United States

Abstract:

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Background:

Ibrutinib, a first-in-class, once-daily BTK inhibitor, is approved in the US for treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The RESONATE-2 study evaluated first-line ibrutinib vs chlorambucil in older patients with CLL/SLL. Objective: Report efficacy and safety with a 5-year median follow-up of first-line ibrutinib in CLL/SLL. Design: Phase 3, international, open-label, randomized study (2013-ongoing) (NCT01722487, NCT01724346). Patients: Patients aged ≥65 with previously untreated CLL/SLL without 17p deletion (N=269). Interventions: Patients randomized 1:1 to ibrutinib 420 mg/day continuously or chlorambucil 0.5–0.8 mg/kg for ≤12 cycles. Patients were eligible to receive ibrutinib after disease progression on chlorambucil. Main Outcome Measures: PFS, ORR by investigator per iwCLL 2008 criteria, and safety. Results: Baseline characteristics were balanced. With a median of 5 years of follow-up (range, 0.1–66 months), PFS benefit continued for ibrutinib vs chlorambucil, with hazard ratio (HR) 0.15 (95% confidence interval [CI]: 0.10–0.22); 60-month PFS estimates for ibrutinib were 70% versus 12% for chlorambucil. Sixty-month OS favored ibrutinib (83%) versus chlorambucil (68%), despite 57% of chlorambucil patients crossing over to ibrutinib. The subgroup of patients with one or more high prognostic risk features of unmutated IGHV, 11q deletion, and/or TP53 mutation had superior outcomes with ibrutinib versus chlorambucil (PFS: HR 0.08 [95% CI: 0.05–0.15]; OS: HR 0.37 [95% CI: 0.18–0.74]). With ibrutinib, ORR including partial response with lymphocytosis was 92%; complete responses increased to 30% (from 11% at the 18-month median follow up). Most common grade ≥3 AEs included neutropenia (13%), pneumonia (12%), and hypertension (8%). Rates of most AEs (any grade) and dose reductions due to grade ≥3 AEs decreased over time. The majority of patients (58%) starting ibrutinib remain on ibrutinib. Patients responded to subsequent therapies, including chemoimmunotherapy and alternate kinase inhibitors, following ibrutinib. Conclusions: Single-agent ibrutinib demonstrated sustained PFS and OS benefit with >5 years of follow up, including for patients with high-risk genomic features. Nearly three-fold more patients achieved CR/CRI. >50% of patients remain on continuous ibrutinib, and no new safety signals have emerged. Funding: Pharmacyclics LLC, an AbbVie Company. Keywords: ibrutinib, long-term follow up, chlorambucil, targeted therapy, CLL, chronic lymphocytic leukemia