Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine Plus Rituximab (BR) Chemoimmunotherapy

Jennifer A. Woyach, Amy S. Ruppert, Nyla A. Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M. Brander, Paul M. Barr, Kerry Rogers, Sameer A. Parikh, Steven Coutre, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry P. Erba, Mark R. Litzow, James S. Blachly, Carolyn Owen, Charles Kuzma, Jeremy S. Abramson, Jennifer R Brown, Richard F. Little, Scott E. Smith, Richard M. Stone, Sumithra J Mandrekar, John C. Byrd

Introduction:

Alliance for Clinical Trials in Oncology A041202 is a NCI National Clinical Trials Network phase 3 study (NCT01886872) comparing BR (Arm 1) with ibrutinib (Arm 2) and the combination of ibrutinib plus rituximab (Arm 3) to determine whether ibrutinib-containing regimens are superior to chemoimmunotherapy (CIT) in terms of progression-free survival (PFS), and whether rituximab adds benefit to ibrutinib therapy. Initial results showed that ibrutinib-containing regimens had superior PFS to CIT, and that rituximab added to ibrutinib did not improve PFS over ibrutinib alone.

Pts and Methods:

Eligible pts on A041202 were those age ≥ 65 years with previously untreated, symptomatic CLL. Pts had a CrCl > 40 mL/min, bilirubin < 1.5 x ULN, and no significant life-limiting intercurrent illness or need for warfarin treatment. Pts were stratified on Rai stage, Zap-70 methylation performed centrally, and del(17)(p13.1) or del(11)(q22.3) by local interphase cytogenetics and were randomized 1:1:1 to each arm. Pts on Arm 1 who progressed could cross over to Arm 2. Here we present an updated analysis after the third planned interim analysis of Arms 2 and 3 versus Arm 1, and at the second planned interim analysis for Arms 3 vs 2. PFS and OS were estimated using the Kaplan-Meier method and corresponding hazard ratios with p-values were estimated using Cox proportional hazards models. These data encompass patient visits through April 2020 and were locked 15 February 2021.

Results:

Between 12/9/2013 and 5/16/2016, 547 pts were randomized (Arms 1: 183, 2: 182, and 3: 182). Baseline characteristics have previously been reported; briefly, median age was 71 years, 53% had unmethylated Zap-70, 61% were IGHV unmutated (performed in 66% of patients), 6% had del(17p) and 20% del(11q) by central FISH. Stimulated karyotype was performed centrally and revealed ≥ 3 abnormalities in 27%, and ≥ 5 in 11% of patients.

With median follow-up of 55 months (mo), median PFS was 44 mo (95% CI 38-54) in Arm 1 and has not been reached in Arms 2 or 3 [Arm 2 vs 1 hazard ratio (HR): 0.36, 95% CI 0.26-0.52, p<0.0001; Arm 3 vs 1 HR 0.36, 95% CI 0.25-0.51, p<0.0001; Arms 3 vs 2 HR 0.99, 95% CI 0.66-1.48, p=0.96]. 48-month PFS estimates were 47%, 76% and 76% in Arms 1, 2, and 3 respectively (Figure 1). At this time, there are no significant differences in overall survival (OS)

among arms (p=0.49). 48-month OS estimates were 84%, 85%, and 86% in Arms 1, 2, and 3, respectively (Figure 2).

The benefit of ibrutinib regimens over CIT, with no additional benefit of rituximab when combined with ibrutinib, was consistent for all subgroups of patients defined by TP53 abnormalities, del(11q), complex karyotype, and IGHV (Figure 3). No significant interaction effects were observed between treatment arm and del(11q), complex karyotype, or IGHV. However, greater benefit of ibrutinib regimens over CIT was observed among patients with TP53 abnormalities than without (p<0.001). Thus in Arm 1, PFS was significantly worse for those with TP53 abnormalities vs without (HR 5.32, 95% CI 3.05-9.27, p<0.0001), but in Arms 2 and 3 combined, there was no significant difference in PFS by presence/absence of TP53 abnormalities (HR 0.99, 95% CI 0.51-1.91, p=0.98).

Notable adverse events with ibrutinib include atrial fibrillation or flutter (afib) and hypertension (HTN). All grade afib was seen in 11 pts on BR (6%) and 67 pts on ibrutinib (19%). All grade HTN was seen in 95 pts on BR (54%) and 263 pts on ibrutinib (73%).

Conclusions:

This update of the A041202 trial continues to show that ibrutinib regimens prolong PFS over BR for older patients with treatment-naïve CLL. With longer follow-up, these benefits continue to be seen across subgroups, including those associated with higher risk disease. Strikingly, within the ibrutinib arms, there does not appear to be inferior PFS for patients with abnormalities in TP53, the highest risk feature seen in CLL, and a predictor of inferior PFS with ibrutinib in relapsed CLL. This differentiates ibrutinib (and perhaps BTKi in general) from other targeted therapy paradigms for treatment-naïve CLL. Similar to prior studies, rates of afib and HTN continue to increase with time on therapy. These data support the use of ibrutinib as initial therapy in CLL, and strengthen the rationale for use of ibrutinib for high risk disease.

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Figure 1

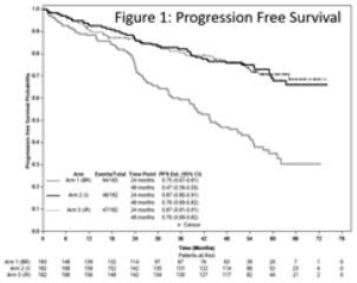
Figure 1: Progression Free Survival

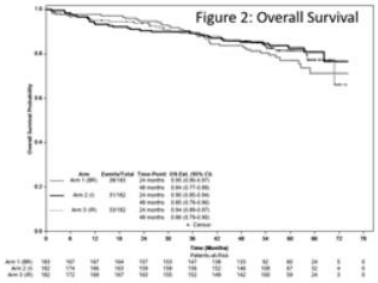
Figure 2: Overall Survival