ELSEVIER

Blood 142 (2023) 437–439

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Ibrutinib Added to Standard Conditioning and As Consolidation Therapy Following Autologous Hematopoietic Stem Cell Transplantation (AutoHCT) for Relapsed/Refractory Activated-B-Cell Subtype Diffuse Large B-Cell Lymphoma (ABC-DLBCL): Primary Analysis of the US Intergroup Double-Blind Randomized Phase III Study Alliance A051301/BMT-CTN 1201

Charalambos Andreadis, MD[1], Olivia Bobek, MS[2], Eric D. Hsi, MD[3], Timothy S. Fenske, MD[4], Susan M. Geyer, PhD[2], Patrick J. Stiff, MD[5], Brian T. Hill, MD PhD[6], Mitchell Horwitz, MD[7], Farhad Khimani, MBBS[8], Richard F. Little, MDMPH[9], Shira N. Dinner, MD[10], Jonathan W. Friedberg, MD MMSc[11], Brad S. Kahl, MD[12], Miguel-Angel Perales, MD[13], Steven M. Devine, MD[14], John P. Leonard[15], Nancy L. Bartlett, MD[16]

[1] Helen Diller Family Comprehensive Cancer Center, UCSF, San Francisco, CA
[2] Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN
[3] Department of Pathology, Wake Forest Baptist Medical Center, Winston Salem, NC
[4] Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI
[5] Division of Hematology and Oncology, Loyola University Medical Center, Maywood, IL
[6] Blood and Marrow Transplant Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[7] Adult Stem Cell Transplant Program, Division of Cellular Therapy, Department of Medicine, Duke University Medical Center, Durham, NC
[8] Department of Blood and Marrow Transplantation and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL
[9] Division of Cancer Prevention, National Cancer Institute, Washington, DC
[10] Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL
[11] Wilmot Cancer Center, University of Rochester, Rochester, NY
[12] Washington University School of Medicine in St. Louis, Saint Louis, MO
[13] Cellular Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY
[14] Be the Match Foundation, Minneapolis, MN
[15] Weill Cornell Medicine, New York, NY
[16] Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

Introduction: AutoHCT is an effective therapy for patients (pts) with DLBCL who are refractory or relapse following first-line chemotherapy, but long term outcomes remain suboptimal. The BTK inhibitor ibrutinib has shown promising activity in pts with ABC-DLBCL (Wilson et al, Nat Med 2015). In 2016 we launched a randomized phase III clinical trial to evaluate the addition of ibrutinib to AutoHCT as part of conditioning and as consolidation therapy for pts with relapsed/refractory ABC-DLBCL.
Patients and Methods: Following assessment of open-label treatment in a safety cohort of 6 pts, we randomly assigned pts with chemotherapy-sensitive persistent or relapsed ABC-DLBCL to receive ibrutinib 560 mg [Arm A] or placebo [Arm B] concurrently with conditioning on days -6 to -1 of AutoHCT (Cycle 1). Following count recovery and resolution of acute toxicities, pts continued ibrutinib 560 mg in Arm A or placebo in Arm B for 12 additional 28-day cycles. Crossover to Arm A using single agent ibrutinib was allowed for pts progressing on Arm B. Central pathology review was performed for disease confirmation and subtype assignment. Initially, ABC subtype assignment was performed using the Nanostring Lymphoma Subtyping Test (LST) but the study was amended to use the IHC-based Hans classifier for non-GCB on 8/15/19. Other key eligibility criteria included receipt of no more than 3 prior regimens, no active CNS involvement, no need for long-term anticoagulation, and no prior progression on Ibrutinib. Pts were stratified by time to relapse (<=12 mos vs >12 mos), type of conditioning (BEAM or CBV) and prior ibrutinib use. The original design required 296 patients with 82% power to detect a difference in 2-year progression-free survival (PFS) rates of 67% vs. 50% with a two-sided alpha of 0.05. A revised statistical design allowed an interim futility analysis to be conducted after 40 pts were enrolled and followed for 2 years. Even though the study met criteria to continue accrual to a target of 160 pts, we decided to close it early due to declining accrual on 12/20/2022. We hereby present the primary analysis of the evaluable patients enrolled (data as of 07/17/2023).

Results: Between 2/6/17 and 8/24/18, we screened 255 pts but enrolled only 34 (13%) largely due to long assay turnaround times and performance characteristics with the LST. Following the switch to the IHC-based Hans classifier (after 8/15/19), 60 out of 110 pts screened were enrolled (54%) in line with our *a priori* expectation. In total, 45 pts were randomized to Arm A vs. 43 to Arm B, with 39 and 38, respectively, being evaluable for the primary endpoint at this time. Median age was 61 years (range 20-75 years), median number of prior lines of therapy was 2, 46% of the pts were female, 21% were refractory or had early relapse, 94% were planned to receive BEAM conditioning. Overall, 87% of pts in Arm A and 88% in Arm B underwent conditioning while 70% and 67% respectively, started maintenance therapy. The median number of cycles received was 6 in Arm A vs. 5 in Arm B. The primary endpoint of 2-year PFS was 57.6% (95% CI: 42.1%, 78.8%) in Arm A vs. 40.8% (95% CI: 26.5, 62.8%) in Arm B (HR=0.54; 95% CI: 0.26, 1.10; log-rank p = 0.087). Median PFS was 26.5 months (95% CI: 10.2, not reached [NR]) in Arm A vs. 8.1 months (95% CI: 5.4, NR) in Arm B. Only one pt crossed over to Arm A after progression on Arm B. The most common grade 3-4 AEs in each of the arms were: neutropenia (A: 14%, B: 14%), febrile neutropenia (A: 11%, B: 9%), and thrombocytopenia (A: 11%, B: 7%). Rates of any grade atrial fibrillation were similar between arms (12.8% in Arm A vs. 10.5% in Arm B); one patient had grade 3 and one patient had grade 4 atrial fibrillation, both in Arm B. Six pts had reported grade 5 events (Arm A: 2 sepsis, 1 COVID-19, 1 respiratory failure and 1 disease progression and Arm B: 1 disease progression) but only one grade 5 event (sepsis, Arm A) was deemed probably related to treatment.

Conclusions: Despite an early high rate of screen failures and declining accruals due to competition with CAR-T cell therapy, the primary analysis suggests that ibrutinib with and following AutoHCT in relapsed/refractory ABC-DLBCL is well-tolerated and may improve PFS in this high-risk patient population.

This trial was supported by: U10CA180821, U10CA180882, U24CA196171; U10CA180820, UG1CA233234 (ECOG-ACRIN); U10CA180868 (NRG); U10CA180888 (SWOG)
ClinicalTrials.gov Identifier: NCT02443077
https://acknowledgments.alliancefound.org

Disclosures Andreadis: *Novartis:* Research Funding; *BMS:* Honoraria, Research Funding; *Gilead:* Honoraria; *Epizyme:* Honoraria; *Astra Zeneca:* Honoraria; *Roche:* Research Funding; *Lilly:* Research Funding; *Merck:* Research Funding; *pharmacyclics:* Honoraria. **Hsi:** *Novartis:* Consultancy. **Fenske:** *Kite (Gilead):* Consultancy, Speakers Bureau; *MorphoSys:* Consultancy, Speakers Bureau; *Pharmacyclics (AbbVie):* Consultancy, Speakers Bureau; *Sanofi:* Consultancy, Speakers Bureau; *SeaGen:* Consultancy, Speakers Bureau; *Servier Pharmaceuticals:* Consultancy, Speakers Bureau; *TG Therapeutics:* Consultancy, Speakers Bureau; *Astrazeneca:* Consultancy, Speakers Bureau; *Beigene:* Consultancy, Speakers Bureau; *Adaptive Biotechnologies:* Consultancy, Speakers Bureau. **Stiff:** *AtaraBiotherapeutics:* Research Funding; *Takeda:* Research Funding; *Macrogenics:* Research Funding; *Incyte Corp:* Research Funding; *Gamida Cell:* Research Funding; *Eisai:* Research Funding; *Amgen:* Research Funding; *CRISPR:* Consultancy. **Hill:** *Kite, a Gilead Company:* Consultancy, Honoraria, Other: travel support, Research Funding; *Genentech:* Consultancy, Other: Advisory board, Research Funding; *Bristol Myers Squibb:* Consultancy; *BeiGene:* Consultancy; *AbbVie:* Consultancy, Other: Advisory board, Research Funding; *AstraZeneca:* Consultancy; *Pharmacyclics:* Consultancy, Other: Advisory board, Research Funding; *Incyte:* Consultancy; *Gilead:* Other: Advisory board. **Dinner:** *Pfizer:* Research Funding; *Rigel:* Research Funding; *BMS:* Research Funding; *Novartis:* Research Funding; *Kite/Gilead:* Research Funding. **Kahl:** *Gilead:* Consultancy, Honoraria; *Genmab:* Consultancy, Honoraria; *Genentech:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria; *Abbvie:* Consultancy, Honoraria; *ADCT:* Consultancy, Honoraria, Research Funding; *Astra Zeneca:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria, Research Funding; *Lilly:* Consultancy, Honoraria. **Perales:** *Incyte:* Consultancy, Honoraria, Research Funding; *Orcabio:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *AbbVie:* Consultancy, Honoraria; *Omeros:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *Kite:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria; *Medigene:* Consultancy, Other; *Sellas Life Sciences:* Consultancy; *VectivBio AG:* Consultancy, Honoraria; *Karyopharm:* Consultancy, Honoraria; *Merck:* Consultancy, Honoraria; *DSMB:* Other; *Miltenyi Biotec:* Honoraria; *Caribou:* Consultancy, Honoraria; *Miltenyi Biotec:* Consultancy, Honoraria, Research Funding; *Allovir:* Consultancy; *Equillium:* Consultancy, Honoraria; *Exevir:* Consultancy, Honoraria; *Syncopation:* Honoraria; *Allogene:* Research Funding; *Servier:* Other; *Cidara Therapeutics:* Consultancy, Other; *Takeda:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *Vor Biopharma:* Consultancy, Honoraria; *Adicet:* Honoraria; *Celgene:* Honoraria; *NexImmune:* Consultancy, Current equity holder in publicly-traded company; *MorphoSys:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *Nektar Therapeutics:* Consultancy, Honoraria, Research Funding. **Leonard:** *National Cancer Institute, Leukemia and Lymphoma Society, Genentech, Epizyme, Janssen:* Research Funding; *AbbVie, AstraZeneca, Astellas, Bayer, BeiGene, BMS, Calithera, Constellation, Eisai, Epizyme, GenMab, Grail, Incyte, Janssen, Karyopharm, Lilly, Merck, Mustang Bio, Pfizer, Roche/Genentech, Seagen, Second Genome, Sutro:* Consultancy. **Bartlett:** *ADC Therapeutics, Foresight Diagnostics, Kite, F. Hoffmann-La Roche Ltd / Genentech, Inc., Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics, Autolus, BMS/Celgene, Forty Seven, Gilead/Kite Pharma, Janssen, Merck, Millennium, Pharmacyclics, F. Hoffmann-La Roche Ltd / Genentech, Inc., Seattle Genetics:* Research Funding; *Washington University School of Medicine:* Current Employment.

OffLabel Disclosure: ibrutinib for diffuse large B cell lymphoma

https://doi.org/10.1182/blood-2023-173742

Figure: Progression-free Survival by Arm

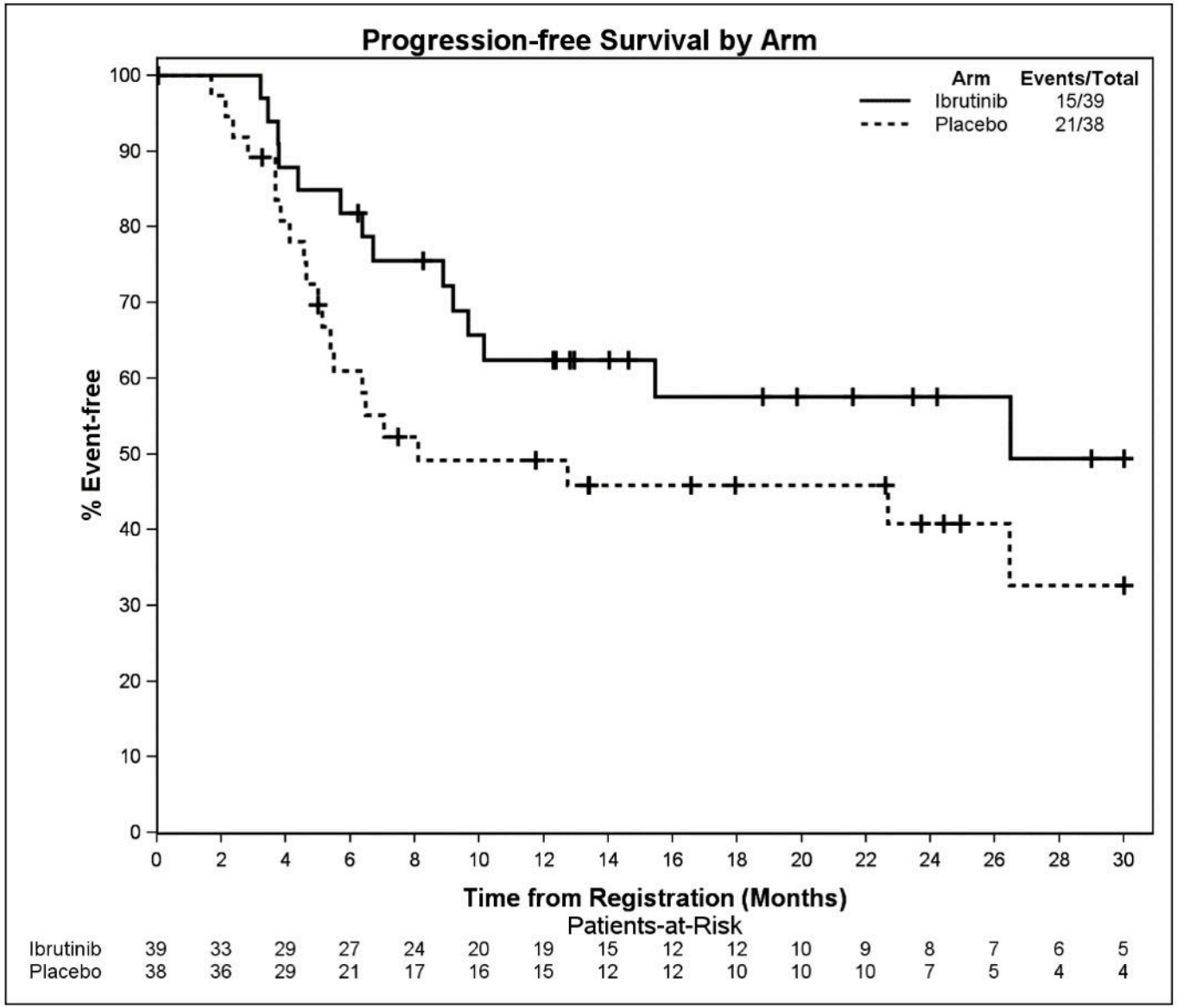

Figure 1