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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Initial Results of a Phase 2 Study of Venetoclax Added to Ibrutinib to Eliminate Ibrutinib Resistance Mutations in CLL

Kerry A Rogers, MD[1], Eric McLaughlin, MS[2], Lai Wei, PhD[2], Seema A Bhat, MD[1], Arianna Crouse, PhD[3], Michael R. Grever, MD[1], Dan Jones, MD[4], Adam S Kittai, MD[1], Gerard Lozanski, MD[4], Mollie Moran, CNP[3], Mark Reid, CNP[3], Ellen J Sass, BS[1], Swetha Suresh, CNP[3], John C. Byrd, MD[5], Jennifer A. Woyach, MD[1]

[1] Division of Hematology, The Ohio State University, Columbus, OH
[2] Center for Biostatistics, The Ohio State University, Columbus, OH
[3] Comprehensive Cancer Center, The Ohio State University, Columbus, OH
[4] Department of Pathology, The Ohio State University, Columbus, OH
[5] Department of Internal Medicine, University of Cincinnati, Cincinnati, OH

INTRODUCTION BTK inhibitors (BTKi) are an important treatment for CLL. As BTKi are given until intolerance or disease progression, resistance is a major challenge. Progressive disease (PD) during BTKi treatment is associated with mutations BTK itself, or the immediate downstream protein, PLCG2. These can be detected 9-12 months prior to PD allowing for intervention. Venetoclax (VEN) is effective after IBR treatment, decreases BTK C481S mutation VAF, and can be combined with IBR. Based on these data, this phase 2 study adding VEN to IBR in patients (pts) with resistance mutations (RMUT) was conducted to test the hypothesis that adding VEN could eliminate molecular resistance.

METHODS CLL pts taking IBR and with a detectable RMUT with or without PD were eligible. Included RMUT were in BTK at C481 and T474 or in PLCG2 at L845, D334, D1140, R665, and S707. Eligible pts continued IBR and added VEN. VEN was given in cycles (C) of 28 days with standard 5-week dose ramp-up to 400mg daily. Response was assessed after C12 and C24 by iwCLL 2008 criteria. Pts achieving a complete remission (CR) or CR with incomplete marrow recovery (CRi) and undetectable minimal residual disease (uMRD) to a level of 10-4 in both blood and marrow discontinued treatment. Those without a uMRD CR/CRi continued through C24 then discontinued if in uMRD CR/CRi. If this response was still not achieved after C24, they stopped IBR and continued VEN alone. Sequencing for RMUT was performed using an assay with a sensitivity of $\geq$0.5% VAF on sorted CD19+ B-cells. The primary endpoint is the rate of undetectable RMUT after C12 of IBR and VEN. Secondary endpoints are rate of uMRD CR/CRi after C12, progression-free (PFS), and overall survival (OS). C12 assessments missed due to the COVID-19 pandemic were considered non-assessable (NA). A second analysis included delayed C12 assessments. Adverse events (AEs) were graded according to the CTCAE v5 except hematologic AEs which used iwCLL criteria. Kaplan Meier methods were used to assess PFS and OS. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Data cut was 7/13/2023.

RESULTS A total of 28 pts were enrolled between 3/2019 and 2/2022 with baseline characteristics in the Table. The median follow up was 31.7 months (range 2.8-47.0) and 8 (29%) pts remain on treatment, 9 (32%) in follow up off treatment, 10 (40%) off study, and 1 (4%) died. BTK C481S testing was available after baseline at time of analysis. After C12, 13/27 (48%) pts who had a BTK C481S mutation at baseline had undetectable BTK C481S (uBTK C481S). This increased to 16/27 (59%) with C12 delayed assessments. 19/27 (70%) pts had uBTK C481S at anytime on study with a median time to uBTK C481S of 6 months (range 2.0-19.8). Of these 6/19 (32%) regained detectable BTK C481S with a median duration of uBTK C481S of 13.8 months (range 5.3-28.8) and 3/6 had PD.
After C12 the overall response rate (ORR) was 71% (4 CR, 4 CRi, 12 partial remissions [PR], 4 stable disease [SD], 1 PD, 3 NA). Including delayed assessments (at C16, C19, and C19), the ORR was 79% (NA->PR n=2, PR->CR n=1). uMRD CR/CRi was attained in 5/28 (18%) and 6/28 (21%) pts after C12 and including delayed assessments, respectively. 12/28 (43%) pts discontinued treatment due to response: 9/28 (32%) in uMRD CR/CRi (C12 n=4, C19 n=1, C25 n=4), 3/28 (11%) electively in

CR with detectable MRD (n=1, C12) or PR with uMRD (n=2, C25). Eight (36%) pts had PD with 1 Richter Transformation. The median PFS and OS were 40.7 months (95% CI: 35.9-not reached) and not reached, respectively (Figure).
Hematologic AEs were frequent with lymphopenia (75%, 46% grade [gr] 3+), thrombocytopenia 68%, 7% gr 3+), neutropenia (61%, 14% gr 3+), and anemia (43%, 0% gr 3+). AEs experienced by >40% of pts were hypocalcemia (75%), diarrhea (75%), weight loss (57%), hypertension (57%), increased lactate dehydrogenase (54%), nausea (54%), dizziness (50%), vomiting (50%), flu like symptoms (43%), and neoplasms (43%). Gr 3 non-hematologic AEs occurring in >10% of pts were hypertension (21%) and diarrhea (14%). Seven (25%) patients had COVID-19 (all gr 2). There were no episodes of tumor lysis syndrome.

CONCLUSION In this phase 2 study, the addition of VEN to IBR decreased the BTK C481S mutation below the detection limit in 59% of pts after 12 cycles of treatment. This combination allowed 32% of pts to discontinue treatment in deep remission. The median PFS (40.7 months) supports further investigation of this approach.

Disclosures Rogers: *AstraZeneca:* Consultancy; *Janssen:* Consultancy; *Loxo@Lilly:* Consultancy; *Novartis:* Research Funding; *Beigene:* Consultancy; *Genentech:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy; *AbbVie:* Consultancy, Research Funding. **Bhat:** *Aptitude Health:* Honoraria; *Abbvie:* Consultancy; *AstraZeneca:* Consultancy, Research Funding. **Kittai:** *Janssen:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *BeiGene:* Consultancy, Research Funding, Speakers Bureau; *Eli Lilly:* Consultancy; *Abbive:* Consultancy; *KITE:* Consultancy; *BMS:* Consultancy. **Byrd:** *Kurome:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Vincerx:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *American Cancer:* Membership on an entity's Board of Directors or advisory committees; *Orbimed:* Consultancy, Research Funding; *Eilean Therapeutics:* Consultancy, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees, Research Funding; *OSU Drug Devel. Inst.:* Consultancy; *Newave:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Orange Grove Bio:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Other: TRAVEL, ACCOMMODATIONS, EXPENSES. **Woyach:** *Newave:* Consultancy; *Loxo:* Consultancy; *Beigene:* Consultancy; *AstraZeneca:* Consultancy; *Abbvie:* Consultancy; *Schrodinger:* Research Funding; *Morphosys:* Research Funding; *Karyopharm:* Research Funding; *Janssen:* Consultancy, Research Funding; *Pharmacyclics:* Consultancy, Research Funding.

TABLE: Baseline Patient Characteristics (n=28)

Age in years, median (range)	62.5 (41-82)
Men, n (%)	20 (71)
White, n (%)	27 (96)
Black, n (%)	1 (4)
Treatments prior to ibrutinib, median (range)	2 (0-13)
IGHV unmutated, n (%)	21 (75)
Complex karyotype ≥3 abnormalities, n(%)	18 (64)
FISH del(17)(p13.1), n (%)	12 (43)
TP53 Mutation, n (%)[1]	14 (50)
Base Laboratory Parameters, median (range)	
Absolute lymphocyte count in k/uL	*3.05 (0.56-154.05)*
Absolute neutrophil count in k/uL	*3.88 (0.69-11.72)*
Hemoglobin in g/dL	*14.1 (8.5-16.7)*
Platelet Count in k/uL	*166 (21-306)*
Resistance Mutations, n (%)	
BTK C481S only	*13 (46)*
BTK C481S + PLCG2	*5 (18)*
BTK C481S + other BTKC481	*5 (18)*
BTK C481S + other BTKC481 + PLCG2	*3 (11)*
BTK C481S + other BTKC481 + BTK L528W[2]	*1 (4)*
PLCG2 only (no BTK mutations)	*1 (4)*

[1]1 missing value. [2]One patient's CLL had BTK mutations including C481S, C481R, C481Y, and L528W with no PLCG2 mutations.

FIGURE: Progression-Free and Overall Survival After Adding Venetoclax

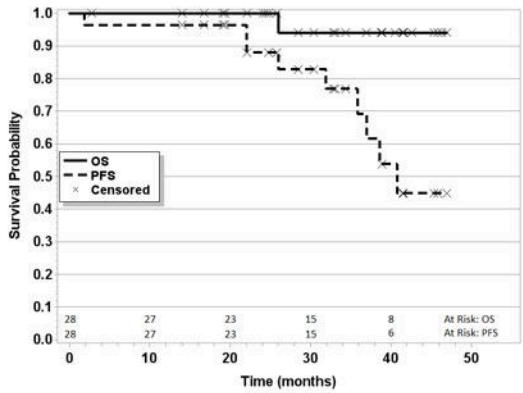

Figure 1

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