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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

A Phase 2 Study of Acalabrutinib, Umbralisib, and Ublituximab (AU2) in Treatment-Naïve and Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

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Background

Targeting the B-cell receptor (BCR) signaling pathway is highly effective for the treatment of CLL. However, attainment of undetectable minimal residual disease (uMRD) is infrequent with current BCR targeting strategies. Here, we report results of a phase 2 study testing time-limited dual BCR inhibitor therapy with a BTK inhibitor acalabrutinib and a PI3Kδ inhibitor umbralisib. With the goal of enhancing depth of remission, a glycoengineered anti-CD20 antibody ublituximab was initiated during Cycle (C) 7.

Methods

In this investigator-sponsored trial, eligible patients with treatment-naïve (TN) or relapsed or refractory (RR) CLL received up to 24 cycles of AU2 (NCT04624633). Each cycle was 28 days. Daily oral doses of acalabrutinib (100mg BID) and umbralisib (800mg QD) began on C1 Day (D) 1. Ublituximab IV began on C7 for 6 cycles (D1, 2, 8, and 15 of C7, D1 of C8-12). Treatment was stopped after C12 if patients achieved complete response (CR) by IWCLL criteria, while all others continued acalabrutinib and umbralisib until C24. In March 2023, umbralisib was withdrawn from drug development, and those who were receiving study therapy at the time continued acalabrutinib alone until C24. The primary endpoint was the CR rate after C24. MRD was assessed in peripheral blood (PB) and bone marrow (BM) using multi-color flow cytometry at 10^{-4}.

Results

The study enrolled 29 patients from December 2020 to January 2022. The median age at enrollment was 63 years (range 40-77). Most patients were male (62%), had TN CLL (72%), and had unmutated IGHV (79%). RR CLL patients had a median of 1 prior line of therapy, most frequently (88%) with chemoimmunotherapy. Genetic alterations were commonly observed at study enrollment, including deletion 17p or *TP53* mutation (21%), deletion 11q or *ATM* mutation (38%), trisomy 12 (24%), and mutations of *NOTCH1*(45%), *SF3B1* (24%), and RAS/RAF pathway (21%). 7% had complex karyotype defined as ≥3 abnormalities.

At a median follow-up of 23 months (range 2-29), with 7 patients still receiving therapy prior to reaching C24, there were no deaths, Richter's transformations, or CLL progression events on the study. The rates of CR, BM uMRD, and PB uMRD at best response were 30%, 44%, and 67%, respectively (Table 1). There were no statistically significant differences in CR and uMRD rates between TN and RR groups at best response. CR and BM uMRD rates improved during the second year of therapy (CR rate: 11% after C12, 28% after C24; BM uMRD rate: 22% after C12, 39% after C24). PB uMRD occurred earlier than BM uMRD, and the rate (44%) remained unchanged between C12 and C24. After completion of study therapy, PB MRD was monitored every 3 months. Five patients had MRD conversion at the end of therapy or shortly after treatment cessation. Median time from the last uMRD to detectable MRD (dMRD) in PB was 3 months (range 3-6). Most (80%, n=4/5) patients with MRD conversion had partial response or dMRD in BM at best response.

Two patients stopped treatment early (due to the diagnosis of second cancer and G4 transaminitis, in 1 patient each). In addition, 7 (24%) patients stopped umbralisib between C15-19 due to discontinuation of drug supply; these patients remained on acalabrutinib monotherapy until C24. All others completed up to 24 cycles of treatment including 3 (10%) patients who stopped therapy per protocol after C12 once CR was achieved. Dose reduction of umbralisib (38%) was more common than acalabrutinib (7%) and was most frequently due to diarrhea (21%) and transaminitis (14%). Only 2 (7%) patients required temporary dose reduction of acalabrutinib to avoid drug-drug interaction. Notable adverse events included diarrhea or colitis (76%, 10% Grade 3 or higher [G≥3]), bruising (69%, 0% G≥3), transaminitis (62%, 17% G≥3), COVID-19 infection (55%, 7% G≥3), hy-

pertension (52%, 10% G≥3), rash (24%, 0% G≥3), and pneumonitis (7%, 3% G≥3). One (3%) patient had *Pneumocystis jirovecii* pneumonia while being off of mandatory prophylaxis due to non-compliance. None had atrial fibrillation.

Conclusions

Dual inhibition of the BCR signaling pathway with up to 2 years of AU2 provided a time-limited treatment option for TN and RR CLL patients. Immune-related adverse events were frequently observed and required dose reduction of umbralisib in 38% of the patients but most were then able to stay on therapy. Longer follow-up is required to determine durability of remission off therapy.

Disclosures Ahn: *BeiGene:* Consultancy; *AstraZeneca:* Consultancy. **Montegaard:** *Abbvie:* Consultancy. **Crombie:** *ADC therapeutics:* Consultancy; *Genmab:* Consultancy; *Roche:* Research Funding; *Merck:* Research Funding; *Abbvie:* Research Funding; *Bayer:* Research Funding; *Karyopharm:* Consultancy; *Kite:* Consultancy; *Incyte:* Consultancy; *Seagen:* Consultancy. **Merryman:** *Epizyme:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Intellia:* Membership on an entity's Board of Directors or advisory committees; *Genmab:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees; *Genentech/Roche:* Research Funding; *Merck:* Research Funding; *Adaptive Biotechnology:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Alphasights:* Membership on an entity's Board of Directors or advisory committees. **Armand:** *Enterome:* Consultancy; *MSD:* Consultancy, Research Funding; *Tessa Therapeutics:* Consultancy; *GenMab:* Consultancy; *ADC Therapeutics:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *Genentech/Roche:* Consultancy, Research Funding; *Xencor:* Consultancy; *Regeneron:* Consultancy; *Foresight Diagnostics:* Consultancy; *IGM:* Research Funding; *Bristol Myers Squibb:* Consultancy, Research Funding; *Merck:* Consultancy, Honoraria, Research Funding; *ATB Therapeutics:* Consultancy; *Affimed Therapeutics:* Research Funding; *Adaptive Biotechnologies:* Research Funding; *Kite - a Gilead company:* Research Funding. **Jacobson:** *Axis:* Speakers Bureau; *Clinical Care Options:* Speakers Bureau; *Precision BioSciences:* Consultancy, Honoraria, Other: Travel support; *Nkarta:* Consultancy, Honoraria; *Humanigen:* Consultancy, Honoraria, Other: Travel support; *AbbVie:* Consultancy, Honoraria; *Daiichi Sanko:* Consultancy, Honoraria; *ImmPACT Bio:* Consultancy, Honoraria; *Instil Bio:* Consultancy, Honoraria; *Bluebird Bio:* Consultancy, Honoraria; *Epizyme:* Consultancy, Honoraria; *Ispen:* Consultancy, Honoraria; *Lonza:* Consultancy, Honoraria, Other: Travel support; *Celgene:* Consultancy, Honoraria, Other: Travel support; *Novartis:* Consultancy, Honoraria, Other: Travel support; *Bristol Myers Squibb:* Consultancy, Honoraria; *Kite, A Gilead Company:* Consultancy, Honoraria, Research Funding. **Davids:** *Eli Lilly:* Consultancy; *Curio Science:* Consultancy; *Merck:* Consultancy; *Janssen:* Consultancy; *Mingsight Pharmaceuticals:* Consultancy; *Research to Practice:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *Ascentage Pharma:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *BMS:* Consultancy; *BeiGene:* Consultancy; *Aptitude Health:* Consultancy; *Adaptive Biosciences:* Consultancy; *ONO Pharmaceuticals:* Consultancy; *Novartis:* Research Funding; *Surface Oncology:* Research Funding; *Secura Bio:* Consultancy; *TG Therapeutics:* Consultancy, Research Funding; *Takeda:* Consultancy; *MEI Pharma:* Research Funding; *AbbVie:* Consultancy, Research Funding. **Brown:** *Alloplex Biotherapeutics:* Consultancy; *Pharmacyclics:* Consultancy; *AbbVie:* Consultancy; *Merck:* Consultancy; *Loxo@Lilly:* Consultancy, Research Funding; *Pfizer:* Consultancy; *Kite:* Consultancy; *Gilead:* Research Funding; *MEI Pharma:* Research Funding; *SecuraBio:* Research Funding; *TG Therapeutics:* Research Funding; *iOnctura:* Consultancy, Research Funding; *Hutchmed:* Consultancy; *Grifols Worldwide Operations:* Consultancy; *Genentech/Roche:* Consultancy; *Beigene:* Consultancy, Research Funding; *Numab Therapeutics:* Consultancy; *Acerta/Astra-Zeneca:* Consultancy.

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Table 1. IWCLL response and MRD status

% (N / N evaluable)	Best response	After C12	After C24
CR, all	30 (8/27)	11 (3/27)	28 (5/18)
TN CLL	32 (6/19)	16 (3/19)	25 (3/12)
RR CLL	25 (2/8)	0 (0/8)	33 (2/6)
BM uMRD, all	44 (12/27)	22 (6/27)	39 (7/18)
TN CLL	53 (10/19)	32 (6/19)	42 (5/12)
RR CLL	25 (2/8)	0 (0/8)	33 (2/6)
PB uMRD, all	67 (18/27)	44 (12/27)	44 (8/18)
TN CLL	79 (15/19)	63 (12/19)	50 (6/12)
RR CLL	38 (3/8)	0 (0/8)	33 (2/6)

Figure 1