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Blood 142 (2023) 3286–3287

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Coronado CLL: A Phase Ib/II Trial of *C*ombination *R*p-3500 and *O*laparib in DNA Damage Repair Pathway *D*eficient Relapsed/Refract *o*ry *C*hronic *L*ymphocytic *L*eukemia

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Background: Genes within the DNA damage repair (**DDR**) pathways are frequently mutated in relapsed/refractory (**R/R**) chronic lymphocytic leukemia (**CLL**) and clinically correlate with decreased response rates and shortened progression-free (**PFS**) and overall survivals (**OS**). The most commonly affected DDR genetic aberrations include deletion 17p13 [**del(17p)**], deletion 11q22.3 [**del(11q)**], and mutations in *TP53*, *ATM*, *SF3B1*, *XPO1* and *POT1*. Due to their poor clinical outcomes, patients (pts) with DDR-deficient CLL remain an area of unmet need and the development of novel drugs and combinations will be critical to improving their prognosis.

Mechanistically, CLL cells with DDR genetic alterations lack double-stranded DNA breakage repair and major cell cycle checkpoint pathways. Therefore, R/R CLL cells are dependent on single-stranded DNA breakage (**SSB**) repair and alternative DNA replication arrest machinery to ensure DNA integrity, strand repair and cell survival. DNA damage at the replication fork is primarily recognized by ataxia telangiectasia and rad3 (**ATR**) protein, which ensures mitotic arrest and recruitment of poly (ADP-ribose) polymerase (**PARP**) based SSB repair mechanisms. In germline DDR-deficient breast and ovarian cancers with *BRCA1/BRCA2* mutations, the use of both single agent PARP inhibitors (**PARPi**) and ATR inhibitors (**ATRi**) have led to significant disease response and improved OS. Furthermore, combination PARPi and ATRi have demonstrated synergistic activity in preclinical data producing increased apoptosis and cell death in BRCA2-mutated ovarian cell lines. In DDR-deficient CLL primary cell and murine models, single agent PARPi and ATRi have demonstrated significant cell death as compared to wildtype CLL and healthy donor lymphocytes.

RP-3500 is a highly potent ATRi. In preclinical data generated in SUM149PT DDR-deficient breast cancer cell lines, combining RP-3500 with the PARPi, olaparib, substantially reduced tumor volume at lower doses than the previously determined maximum tolerated dose (**MTD**) of each drug when used as monotherapy. Furthermore, intermittent dosing of both drugs (3 days per week) demonstrated equal cell apoptosis as continuous dosing. Therefore, we *hypothesize* that the combination of RP-3500 and olaparib will be a highly efficacious treatment for R/R DDR-deficient CLL pts and that the lower dosages and intermittent dosing schedule required of each drug when administered in combination will improve safety of the treatment.

Study Design and Methods: This is a multi-site (University of Utah and the Ohio State University), phase Ib/II investigator-initiated clinical trial using combination RP-3500 and olaparib in R/R CLL pts with DDR pathway deficiencies to determine the safety and efficacy of the drug combination (NCT05405309). Primary objectives include determining the MTD in phase Ib leading to the recommended phase 2 dose (**RP2D**), and overall response rate (**ORR**) in phase II. Key secondary objectives include safety and tolerability, PFS, OS and duration of response of the combination.

Eligibility: Key inclusion criteria include a diagnosis of CLL according to the 2018 iwCLL guidelines, age ≥18 years, ECOG performance status of ≤2, R/R after at least 2 prior lines of therapy. Primary CLL cells must exhibit any one of the following abnormalities: a) somatic mutation(s) in *TP53, ATM, SF3B1, XPO1* or *POT1*, or b) positive FISH for either del(17p) or del(11q).

Statistical Methods: ***Phase Ib****: The* phase Ib of the trial will utilizea keyboard design, which is a novel Bayesian method that typically underestimates the MTD. The target toxicity is 30% with an equivalence interval between 25-33% of pts. With an anticipated 3 dose levels (**DL**) and an option for a DL-1, up to 18 pts may be required to determine the MTD and RP2D.

Phase II: Any pt treated at the RP2D within phase Ib will be rolled into the phase II analysis for efficacy. With a planned 24 evaluable pts in phase II, the target ORR will be 60%, which was selected due to a recent phase I/II study of pirtobrutinib enrolling a similar CLL pt population demonstrating an ORR of the drug ~63%. ORR will be summarized by the observed proportion and an exact one-sided 95% confidence interval (Clopper-Pearson method). With 24 evaluable pts, the lower

bound of the confidence interval will be approximately 17-20% below the observed proportion for observed ORR near 60%, which is an acceptable level of precision in a dose expansion cohort.

Disclosures Kittai: *Abbive:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *BeiGene:* Consultancy, Research Funding, Speakers Bureau; *Eli Lilly:* Consultancy; *Janssen:* Consultancy; *KITE:* Consultancy; *BMS:* Consultancy. **Stephens:** *AbbVie:* Consultancy; *AstraZeneca:* Consultancy, Research Funding; *BeiGene:* Consultancy; *Bristol-Myers Squibb:* Consultancy; *Celgene:* Consultancy; *Genentech:* Consultancy; *Janssen:* Consultancy; *Lilly:* Consultancy; *Novartis:* Research Funding.

https://doi.org/10.1182/blood-2023-178381