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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Fixed-Duration Pirtobrutinib Combined with Venetoclax ± Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia: Updated Results, Including MRD Data, from the BRUIN Phase 1b Study

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Background: Covalent (c) Bruton tyrosine kinase inhibitors (BTKi) have transformed the management of chronic lymphocytic leukemia (CLL). Recent clinical studies have evaluated the safety and efficacy of fixed-duration regimens with venetoclax and cBTKi. While these combinations are effective, their use may be limited by toxicity. Pirtobrutinib, a highly selective, non-covalent (reversible) BTKi, has shown promising safety and efficacy in heavily pretreated relapsed or refractory (R/R) CLL patients (pts). Here, we report the safety and efficacy of fixed-duration pirtobrutinib combined with venetoclax ± rituximab in pts with R/R CLL.

Methods: Pts with R/R CLL were eligible for pirtobrutinib combined with venetoclax ± rituximab in the phase 1b portion of the multicenter phase 1/2 BRUIN study (NCT03740529). Prior cBTKi therapy was allowed, but not prior venetoclax. Pts were enrolled into sequential cohorts, first in the pirtobrutinib + venetoclax (PV) cohort and then the PV + rituximab (PVR) cohort. Pirtobrutinib 200 mg QD was started on cycle 1 day 1, and venetoclax was started on cycle 2 day 1 with the standard 5-week dose ramp to 400 mg QD target dose. PV was given for up to 24 cycles; each cycle was 28 days. For the PVR cohort, rituximab was given at 375 mg/m ^{2} on cycle 1 day 1 and then 500 mg/m ^{2} on day 1 of cycles 2-6. The primary endpoint was safety as assessed by treatment-emergent adverse events (TEAEs) graded according to CTCAE v5.0. Other key endpoints included overall response rate (ORR), progression-free survival (PFS), and minimal residual disease (MRD). Undetectable MRD (uMRD) was defined as less than 1 CLL cell/10,000 nucleated cells ($<1x10^{-4}$) in peripheral blood by ClonoSEQ® assay (Adaptive Biotechnologies, Seattle, WA). A data cut of May 5, 2023, was utilized.

Results: Fifteen pts received PV, and 10 received PVR. Median age was 66 years (range, 49-77) for those who received PV and 69 (range, 39-78) for those who received PVR. Median prior lines of therapy was 1 (range, 1-2) for the PV cohort and 2 (range 1-4) for the PVR cohort. Most pts had received prior chemotherapy (PV=53%; PVR=60%), CD20 monoclonal antibody (73%; 70%), and cBTKi (73%; 60%). The majority of pts had IGHV unmutated CLL (PV=73%; PVR=89%). ORR was 93.3% (95% CI, 68.1-99.8) for the 15 pts receiving PV and 100% (95% CI, 69.2-100.0) for the 10 pts receiving PVR, with 10 complete responses (PV=7; PVR=3). Median duration of follow-up for PFS was 22.1 months (IQR, 20.1-25.7) for PV and 22.1 months (IQR, 20.7-22.1) for PVR; PFS at 18 months was 92.9% (95% CI, 59.1-99.0) for the 15 pts receiving PV and 80.0% (95% CI, 40.9-94.6) for the 10 pts receiving PVR. The overall uMRD rate at cycle 13 was 70.8% (PV=10; PVR=7) for the 24 evaluable pts, with 87.5% (PV=12; PVR=9) of pts achieving uMRD at some time during the trial and all but one pt sustaining uMRD during subsequent MRD assessments (**Figure**). Twenty-two pts discontinued treatment (PV=14; PVR=8); of these, 14 completed all 24 cycles of therapy (PV=9; PVR=5) and 8 discontinued early because of progressive disease (PV=2), adverse events (PVR=2), protocol noncompliance (PV=1), death unrelated to treatment (PVR=1), or other reasons (PV=2). Three pts (PV=1; PVR=2) continue to

receive treatment. The median relative dose intensity was similar in both cohorts (PV=97.9%; PVR=98.6%). The most common TEAE of any grade included nausea (PV=60.0%; PVR=40.0%), fatigue (53.3%; 50.0%), and diarrhea (46.7%; 60.0%). The most common grade ≥3 TEAE was neutropenia/neutrophil count decreased (PV=46.7%; PVR=60.0%). Grade ≥3 clinical tumor lysis syndrome occurred during venetoclax dose escalation (PV=2), including a grade 3 case that resolved spontaneously after 24 hours and a grade 4 case that resolved after short-term intravenous fluids. Treatment-related adverse events led to dose reductions in three pts (PV=1; PVR=2) and treatment discontinuation in two pts (PVR=2).

Conclusions: Fixed-duration pirtobrutinib combined with venetoclax ± rituximab was well tolerated and demonstrated sufficiently promising efficacy to warrant further investigation in pts with R/R CLL. The BRUIN CLL-322 phase 3 trial comparing PVR vs VR in previously treated CLL is currently enrolling pts (NCT04965493).

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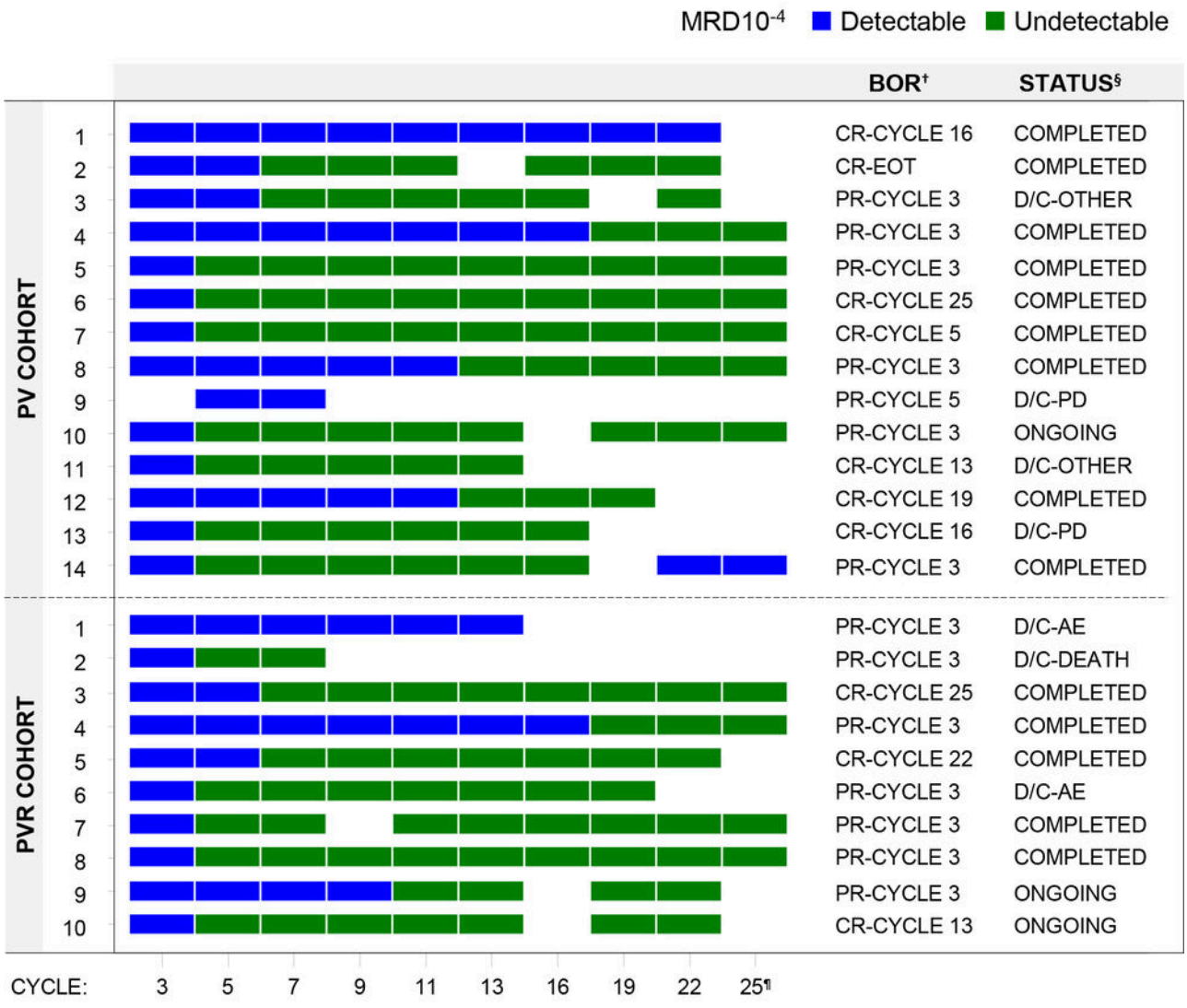
OffLabel Disclosure: Pirtobrutinib is approved in the USA for treatment of relapsed or refractory MCL after at least 2 lines of systemic therapy, including prior BTKi.

Figure: Swimmer's Plot of MRD and Best Overall Response to Fixed-duration Pirtobrutinib in Combination with Venetoclax ± Rituximab in R/R CLL



† Best overall response was based on investigator assessment.

§ One patient in the PV cohort discontinued treatment because of protocol noncompliance. The calibration sample (i.e., pre-treatment) for this patient failed to identify a clonal sequence and subsequent MRD tracking by clonoSEQ was not possible. MRD data are therefore missing for this patient and not presented in the figure.

¶ Study protocol required a lead-in cycle of pirtobrutinib monotherapy followed by up to 24 cycles of combination therapy with venetoclax, for a total of 25 cycles.

Abbreviations: AE, adverse event; BOR, best overall response; CR, complete response; D/C, discontinued; MRD, minimal residual disease; PD, progressive disease; PR, partial response

Figure 1

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