Abstract: S164

Title: COMBINED PIRTOBRUTINIB, VENETOCLAX, AND OBINUTUZUMAB IN FIRST-LINE TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PHASE 2 TRIAL

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Session Title: Frontline therapy for CLL and Richter

Background:

Treatment with combined covalent BTK-inhibitor (cBTKi such as ibrutinib, acalabrutinib, zanubrutinib) with BCL2-inhibitor, venetoclax +/- CD20 monoclonal antibody obinutuzumab showed high rates of undetectable MRD (U-MRD) remission in patients (pts) with CLL (Jain, NEJM 2019; Munir NEJM 2023; Wierda, JCO 2021; Kater, NEJM Evidence 2022).

Aims:

We report the first results of time-limited, combined non-covalent BTKi, pirtobrutinib, with venetoclax and obinutuzumab as first-line treatment for pts with CLL (NCT05536349).

Methods:

Pts with previously untreated CLL meeting iwCLL treatment criteria were enrolled. Pts received pirtobrutinib 200mg daily starting Cycle 1 Day 1 (C1D1) continuously until end of C13. Obinutuzumab was given as standard 6 cycles starting C1D1. Venetoclax standard ramp-up was initiated C2D1 to the target dose of 400mg daily and continued until end of C13. Response evaluations (iwCLL 2018 criteria) were done by imaging and bone marrow assessment at the end of C7 (6-month of the triplet combination) and C13. Each cycle is 28 days. MRD was assessed by ClonoSEQ next-generation sequencing in both peripheral blood and bone marrow at the end of C7 and C13. Pts with detectable MRD (≥10-5 in either blood or marrow) at the end of C13 can continue pirtobrutinib and venetoclax for another 12 cycles per protocol. All pts, once off therapy, will be monitored by peripheral blood MRD by NGS every 3 months for the first 12 months off therapy, and then every 6 months. Primary endpoint is to estimate the bone marrow U-MRD rate at the end of C7.

Results:

Between February 2023 and September 2023, a total of 40 pts were enrolled. Median age is 64 years (range, 38-76 years). 75% had IGHV-unmutated CLL. 10% had del(17p)/TP53 mutation. Pretreatment characteristics are shown in Table 1.

1 pt came off trial during C3 for treatment of newly-diagnosed head/neck cancer; the remaining 39 pts continue on the trial. The median follow-up is 7.5 months.

At the end of C7, among the 25 pts who reached this time-point, bone marrow NGS showed U-MRD at 10-6 sensitivity in 19/25 (76%) [detectable MRD ≥10-6 but <10-4 was seen in 4/25 pts; 2 pts had MRD ≥10-4]. Peripheral blood NGS MRD at the end of C7 among these 25 pts showed U-MRD at 10-6 sensitivity in 22/25 (88%) [detectable MRD ≥10-6 but <10-4 was seen in 2 pts; 1 pt had MRD ≥10-4].

Grade 3-4 neutropenia and thrombocytopenia occurred in 58% and 15% pts, respectively. 53% pts required G-CSF. 3 pts had neutropenic fever. Dose reduction of pirtobrutinib and venetoclax occurred in 25% and 23%, respectively (most commonly due to neutropenia).

No pt has progressed/died.

Summary/Conclusion:

We report the first results for first-line combined pirtobrutinib, venetoclax, and obinutuzumab in pts with CLL. A

very high rate of bone marrow U-MRD at 10-6 sensitivity was noted at 6-months of combined treatment. Adverse event profile was similar to what was noted in previous studies with these agents. Updated data including end of C13 assessment will be presented.

	n (%) or median [range], N=40
Age, years	**
Gender, M	
ALC, K/µL	
PLT, K/µL	
HGB, g/dL	
B2M, mg/L	
FISH (Dohner hierarchical classification)	**Del(17p)**
	Del(11q)
	Trisomy 12
	None
	Del(13q)
IGHV status	**Unmutated**
	Mutated
Mutations	***NOTCH1***
	SF3B1
	KRAS/NRAS
	BIRC3
	TP53
Del(17p) / *TP53*-mutated	

Keywords: B-CLL, BCL2, Bruton’s tyrosine kinase inhibitor (BTKi), CD20