Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated patients with chronic lymphocytic leukemia: Impact of early MRD kinetics on posttreatment outcomes

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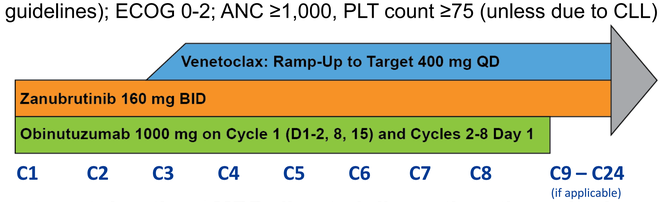
Introduction

- Venetoclax plus obinutuzumab achieves frequent uMRD.[1-2]
- Zanubrutinib is a second-generation BTKi with fewer cardiac AEs and superior PFS compared with ibrutinib in relapsed or refractory CLL.[2]
- BCL2i/BTKi combinations appear synergistic with frequent uMRD, but grade >3 neutropenia occur in 33-56%.[4-5]
- Zanubrutinib, obinutuzumab, and venetoclax (BOVen) appeared well-tolerated and met its primary endpoint achieving frequent uMRD in previously untreated pts with CLL.[6]
- Longer follow-up needed to evaluate MRD-driven treatment strategy.

Methods and Patients

- Multicenter, investigator-initiated, phase 2 study
- Key eligibility criteria: Treatment naïve CLL/SLL; Requires treatment (iwCLL guidelines); ECOG 0-2; ANC ≥1,000, PLT count ≥75 (unless due to CLL)



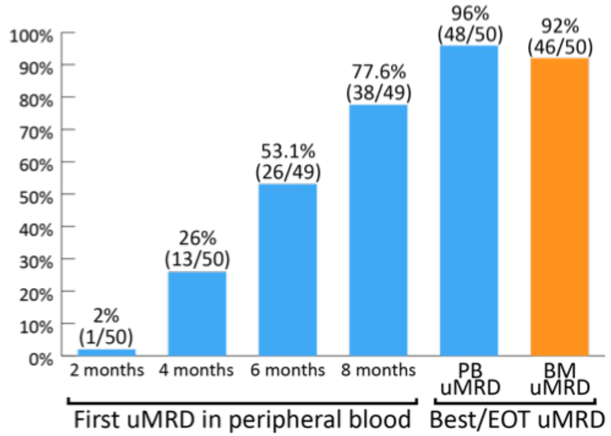
Treatment duration / MRD-directed discontinuation criteria

- Treatment duration: Min 8 months to Max 24 months (including 2-month doublet lead-in prior to venetoclax)
- Peripheral blood MRD (flow cytometry) assessed every 2 cycles
  - If PB uMRD <10^{-4} (flow), then BM MRD assessment within 14 days
  - If PB and BM uMRD <10^{-4} (flow), repeat PB MRD assessment after 2 additional cycles
  - If PB x 2 (consecutively) and BM uMRD <10^{-4} (primary endpoint), treatment is discontinued

Baseline Patient Characteristics

	N=52
Enrollment periods	03/2019 to 10/2019 (Primary Cohort; n=39) 07/2020 to 04/2021 (Expansion; n=13)
Median follow-up (mo)	40 months (4.1-47.4+)
Age (years)	62 years (23-77)
Sex (Male:Female)	3:1
IGHV unmutated/germline	71% (37/52)
TP53 mutation and/or 17p deletion	17% (9/52)

MRD response (flow cytometry, <10^{-4})



- 96% (48/50) uMRD in PB
- 92% (46/50) uMRD in both PB and BM
- Median time on treatment 10 mo (IQR 8-12 mo)

Adverse events (all cause)

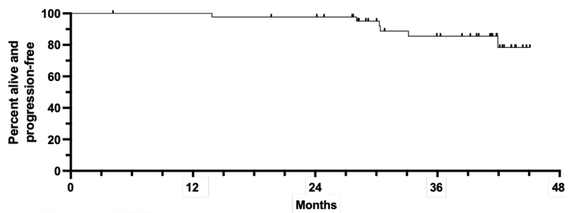
Grade ≥3 AEs in ≥2 pts*	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Neutrophil count decreased	5 (10%)	7 (13%)	-
Platelet count decreased	4 (8%)	-	-
Lung infection	3 (6%)	-	-
Infusion related reaction	1 (2%)	1 (2%)	-
Rash, maculopapular	2 (4%)	-	-
Skin infection	2 (4%)	-	-

•Additional Grade ≥3 AEs occurring in 1 patient each are as follows: One grade 5 AE occurred in a patient with intracranial hemorrhage on cycle 1 day 1. Grade 3 AEs were febrile neutropenia, fatigue, diarrhea, headache, alkaline phosphatase increased, mucositis oral, hypophosphatemia, bilirubin increased, heart failure, purpura, rash, gallbladder obstruction, left Achilles partial tear, and invasive mammary carcinoma (1 patient each).

Any grade AEs in ≥20% pts	Gr 1-2 (%)	Gr 3 (%)	Gr 4 (%)
Platelet count decreased	25 (48%)	4 (8%)	-
Fatigue	28 (54%)	1 (2%)	-
Neutrophils decreased	16 (31%)	5 (10%)	7 (13%)
Diarrhea	23 (44%)	1 (2%)	-
Bruising	23 (44%)	-	-
Cough	20 (38%)	-	-
Infusion related reaction	17 (33%)	1 (2%)	1 (2%)
Nausea	18 (35%)	-	-
Anemia	18 (35%)	-	-
Constipation	17 (33%)	-	-
Arthralgias	13 (25%)	-	-
Rash, maculopapular	10 (19%)	2 (4%)	-
Nasal congestion	12 (23%)	-	-
GERD	12 (23%)	-	-

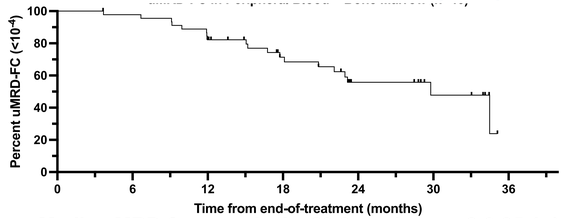
BOVen with uMRD-directed treatment duration resulted in durable PFS and uMRD

Progression-Free Survival in All Pts (n=50)



- **Median PFS – not reached (range, 4.1-45.1+)**
- Time 0 = Treatment Start
- Calculated from Treatment Start until PD/death or last follow-up (patients entering retreatment based on MRD criteria without iwCLL PD were censored).

MRD-Free Survival in BM uMRD Pts (n=46)



- **Median MRD-free survival – 29.8 mo (range, 3.6-35.1+)**
- Time 0 = End-of-Treatment in uMRD <10^{-4} (flow)
- Calculated from EOT until date of detectable MRD ≥10^{-4} or last confirmed uMRD <10^{-4} (flow)

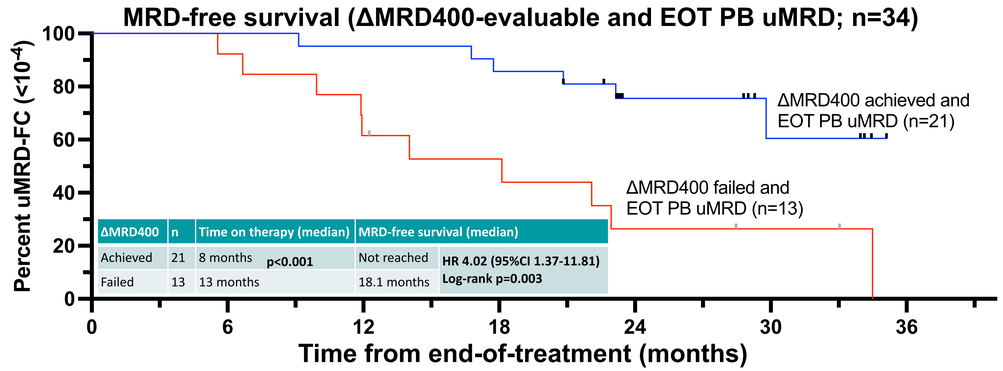
ΔMRD400 was associated with longer MRD-free survival despite shorter time on therapy

- ΔMRD is decrease in PB MRD (Immunosequencing) at C5D1 (1 mo after reaching target venetoclax dose)

ΔMRD400	BM uMRD in ≤8 mo	Time to BM uMRD	Time on therapy
Achieved (n=21)	100% (21/21)	6 mo (IQR 6-6)	8 mo (IQR 8-10)
Failed (n=14)	21% (3/14)	11 mo (IQR 10-15.5)	13 mo (IQR 12-17.5)

≥400-fold reduction identified as the optimal cutoff for predicting uMRD <10^{-4} within 8 months (Youden Index)

MRD-free survival (ΔMRD400-evaluable and EOT PB uMRD; n=34)



Conclusions

- BOVen was well tolerated with no additional safety signals with long-term follow-up
- BOVen achieved frequent uMRD (<10^{-4}) in blood (96%) and bone marrow (92%) and durable progression-free survival
- Median duration of therapy was 10 months (IQR 8-12) including 2-month lead-in
- MRD-free survival (<10^{-4}) was 29.8 months: Longer among those who achieved ΔMRD400 (NR vs 18.1 mo, log-rank p=0.003) despite fewer cycles of therapy (8 vs 13 cycles, p<0.001)
- **Phase II trial of BOVen in TN CLL/SLL with ΔMRD400-directed therapy (24 vs 10 mo) – MSKCC, MGH, Northwestern**
  Hypothesis: Longer treatment duration for pts who fail to achieve ΔMRD400 will further improve uMRD duration in these pts

References: 1: Fischer, N Eng J Med 2019; 2: Al-Sawaf, J Clin Oncol 2021; 3: Brown, N Eng J Med 2023; 4: Rogers, J Clin Oncol 2020; 5: Davids, Lancet Oncol 2021; 6: Soumerai, Lancet Haem 2021

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