Multicenter Phase II Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Treatment-Naïve Chronic Lymphocytic Leukemia: 5-Year Follow up, Retreatment Outcomes, and Impact of MRD Kinetics (ΔMRD400)

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Introduction

- Venetoclax-obinutuzumab achieves frequent uMRD in treatment-naïve (TN) CLL/SLL, and an MRD4-free survival of 21.7 months among patients who achieve uMRD4 in BM.[1-2]
- Zanubrutinib has favorable safety profile with fewer cardiac AEs, and superior PFS compared with ibrutinib in relapsed/refractory (R/R) CLL/SLL.[2]
- BCL2i/BTKi combinations appear synergistic and can achieve durable uMRD.[4-5]
- Zanubrutinib, obinutuzumab, and venetoclax (BOVen) appeared well-tolerated and achieved frequent uMRD in TN CLL/SLL.[6]
- **Herein, we present long-term follow-up of BOVen in TN CLL/SLL, preliminary safety and efficacy of retreatment with zanubrutinib-venetoclax, and the impact of response kinetics (ΔMRD400) on outcomes.**

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)

Enrollment periods	03/2019 to 10/2019 (Primary Cohort; n=39) 07/2020 to 04/2021 (Expansion; n=13)
Median follow-up (mo)	57 months (4-63+)
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)
Evaluable for efficacy	50

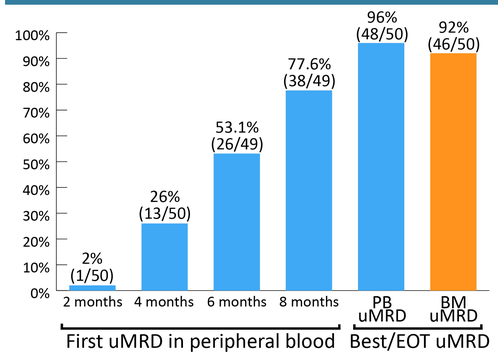
Adverse Events (All-Cause)

Any Grade AEs in ≥15% pts	Gr 1-2 (%)	Gr 3 (%)	Gr 4 (%)
Platelet count decreased	27 (52%)	4 (8%)	
Fatigue	30 (58%)	1 (2%)	
Neutrophil count decreased	16 (31%)	4 (8%)	10 (19%)
Diarrhea	25 (48%)	2 (4%)	-
Bruising	25 (48%)	-	-
Cough	20 (39%)	-	-
Infusion related reaction	17 (33%)	2 (4%)	1 (2%)
Nausea	19 (37%)	-	-
Anemia	19 (37%)	-	-
Constipation	18 (35%)	-	-
Nasal congestion	15 (29%)	-	-
Rash	11 (21%)	2 (4%)	-
Insomnia	12 (23%)	-	-
Myalgia	12 (23%)	-	-
GERD	12 (23%)	-	-
Arthralgia	11 (21%)	-	-
AST increased	10 (19%)	-	-
Dyspnea	10 (19%)	-	-
Dizziness	9 (17%)	-	-
Abdominal pain	9 (17%)	-	-
Alkaline phosphatase increased	7 (14%)	1 (2%)	-
Headache	7 (14%)	1 (2%)	-
Postnasal drip	8 (15%)	-	-
Sore throat	8 (15%)	-	-
Hypocalcemia	8 (15%)	-	-
Sinusitis	8 (15%)	-	-

Grade ≥3 AEs in ≥2 pts	Gr 3 (%)	Gr 4 (%)	Gr 5 (%)
Neutrophil count decreased	4 (8%)	10 (19%)	-
Platelet count decreased	4 (8%)	-	-
Lung infection	3 (6%)	-	-
Diarrhea	2 (4%)	-	-
Infusion related reaction	1 (2%)	1 (2%)	-
Rash	2 (4%)	-	-
Skin infection	2 (4%)	-	-
Fatigue	1 (2%)	-	-
Alkaline phosphatase increased	1 (2%)	-	-
Headache	1 (2%)	-	-
Mucositis oral	1 (2%)	-	-
Atrial fibrillation	-	1 (2%)	-
Hypophosphatemia	1 (2%)	-	-
Rash	1 (2%)	-	-
Blood bilirubin increased	1 (2%)	-	-
Heart failure	1 (2%)	-	-
Purpura	1 (2%)	-	-

- No laboratory or clinical tumor lysis syndrome (Howard criteria).
- Additional Grade ≥3 AEs in 1 patient each as follows: One grade 5 AE occurred in a patient with intracranial hemorrhage on cycle 1 day 1, one grade 3 febrile neutropenia, and one Achilles tendon partial tear.

MRD4 outcomes



- uMRD4 = MRD $<10^{-4}$ (flow)
- 96% (48/50) uMRD4 in PB
- 92% (46/50) uMRD4 in both PB and BM (primary endpoint).
  - All 46 met prespecified treatment discontinuation criterion and stopped therapy after a median of 10 mo (IQR 8-12 mo)

ΔMRD400 predicts MRD4 outcomes

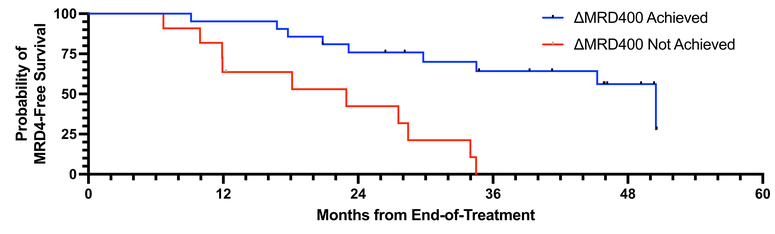
- ΔMRD is decrease in PB MRD (Immunosequencing) at C5D1 (after 1 month of ven at 400 mg)
- 400-fold reduction in MRD level the optimal cutoff to predict BM uMRD4 within 8 mo (Youden)

ΔMRD400	BM uMRD within 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)

- ΔMRD400 does not appear to track with traditional risk factors (e.g., TP53 and IGHV)

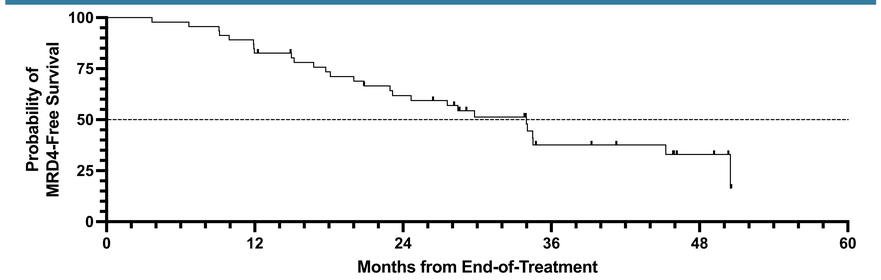
ΔMRD400	Del(17p) / TP53 mut (n=5)	IGHV unmutated (n=25)
Achieved	4 (80%)	15 (60%)
Failed	1 (20%)	10 (40%)

ΔMRD400 a/w longer MRD4-free survival despite less therapy



ΔMRD400	Number patients (%)	Time on therapy (median)		MRD4-free survival (median)	
Achieved	21 (60%)	8 months	p<0.001	51 months	HR 4.5 (95% CI 1.5-14.1) Log-rank p<0.001
Failed	13 (40%)	13 months		23 months	

BOVen resulted in durable uMRD4



- **Median MRD4-free survival of 92% (46/50) achieving BM uMRD4: 34 mo (95% CI 23 – NR)**
- MRD4-free survival was calculated from End-of-Treatment until date of +MRD4 or last confirmed uMRD4
- Reference: Ven-O in TN CLL – median MRD4-free survival in patients with BM uMRD4 was 21.7 months[2]

Retreatment with Zanubrutinib and Venetoclax

	N=16
Median retreatment follow-up (mo)	14 months (1-38+)
Median treatment-free interval prior to retreatment (mo)	29 months (7-54)
Protocol-defined retreatment criteria	16 (100%)
MRD ≥1% without increased LN/spleen	4 (25%)
MRD ≥1% with increased LN/spleen	12 (75%)
IGHV unmutated/germline	15 (95%)
TP53 mutation and/or 17p deletion	4 (25%)
Present prior to initial therapy	3
Acquired prior to retreatment	1
ΔMRD400 with BOVen initial therapy	
Achieved	5 (31%)
Failed	8 (50%)
Not available	3 (19%)
Evaluable for iwCLL and MRD response	
iwCLL response assessment	12 (75%)
MRD response assessment	13 (81%)

- **Protocol-defined retreatment criteria:**
  - MRD criteria: MRD ≥1% with characteristic phenotype of CLL in peripheral blood, confirmed ≥28 days later.
  - Tissue criteria: Increased LN, spleen, or extramedullary CLL (histologically-confirmed).
  *** Does not require iwCLL progression.*
- **Retreatment plan:** Zanubrutinib-venetoclax for 12-24 cycles (Discontinue after 12 cycles if uMRD4 in PB and BM)
- **iwCLL overall response rate (n=12):** 92% (11/12)
- **PB uMRD4 response rate (n=13):** 46% (6/13)
- **ΔMRD400 and retreatment uMRD4:** Patients who achieved ΔMRD400 with initial BOVen therapy appeared more likely to achieve PB uMRD with retreatment: 75% (3/4) vs 29 (2/7)

Any grade AEs in ≥10% pts	Gr 1-2 (%)	Gr 3 (%)	Gr 4 (%)
Upper respiratory infection	7 (44%)	-	-
COVID-19	6 (38%)	-	-
Cough	4 (25%)	-	-
Diarrhea	4 (25%)	-	-
Fatigue	4 (25%)	-	-
Hyperkalemia	3 (19%)	-	-
Influenza	3 (19%)	-	-
Bruising	2 (13%)	-	-
Headache	2 (13%)	-	-
Nasal congestion	2 (13%)	-	-
Nausea	2 (13%)	-	-
Night sweats	2 (13%)	-	-
Platelet count decreased	2 (13%)	-	-

- One patient had grade 3 neutropenia with retreatment

Conclusions

- BOVen was well tolerated with no additional safety signals with long-term follow-up
- BOVen achieved frequent uMRD4 in peripheral blood (96%) and bone marrow (92%)
- MRD4-free survival was 34 months from end-of-treatment and was longer among those who achieved ΔMRD400 (51 vs 23 mo, log-rank p<0.001) despite fewer cycles of therapy
- Retreatment with zanubrutinib-venetoclax resulted in iwCLL response in 92% (11/12) and PB uMRD4 in 46% (6/13)
- **Ongoing:** Phase II trial of BOVen with ΔMRD400-directed therapy in TN CLL (24 vs 10 mo)
  - Hypothesis: Longer duration of therapy for patients who fail to achieve ΔMRD400 will further improve uMRD duration in these patients

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