Long-term follow-up of multicenter phase II trial of zanubrutinib, obinutuzumab, and venetoclax (BOVen) in previously untreated patients with CLL/SLL

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Background

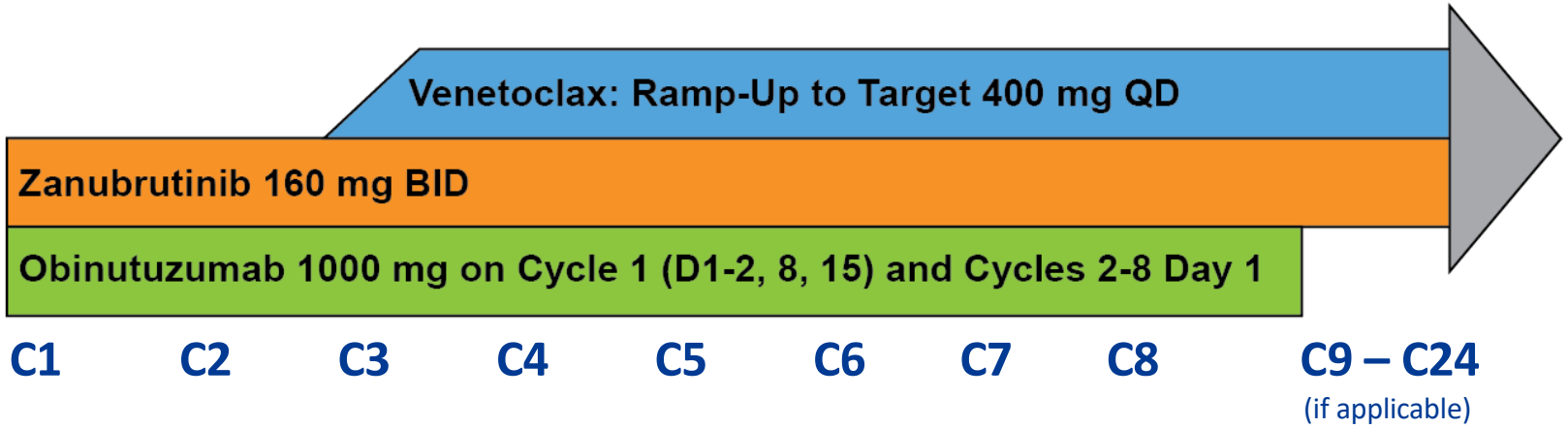
- Venetoclax-Obinutuzumab achieves frequent uMRD.[1-2]
- Zanubrutinib is a second-generation BTKi with fewer cardiac AEs and superior PFS compared with ibrutinib in relapsed or refractory CLL.[2]
- BCL2i/BTKi combinations appear synergistic with frequent uMRD, but grade >3 neutropenia occur in 33-56%.[4-5]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

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

Study design and criteria for treatment discontinuation

Key eligibility criteria

Previously untreated CLL/SLL
Requires treatment (iwCLL guidelines)
ECOG 0-2
ANC ≥1,000, PLT count ≥75 (unless due to CLL)
Coumadin and dual antiplatelet excluded



Treatment duration / MRD-directed treatment 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), then repeat PB MRD assessment after 2 additional cycles
  - If PB x 2 (consecutively) and BM uMRD $<10^{-4}$ (primary endpoint), treatment is discontinued

Patient demographics

	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)

- All 52 patients are evaluable for safety analyses and 50 patients are evaluable for efficacy analyses
- Two patients received fewer than two cycles of therapy because of intracranial hemorrhage occurring on cycle 1 day 1 (n=1), and metastatic adenocarcinoma on cycle 1 day 25 (n=1) and did not undergo MRD or response assessment.

Adverse events (all-cause)

Any grade AEs in ≥10% pts	Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)
Platelet count decreased	25 (48%)	4 (8%)	-
Fatigue	28 (54%)	1 (2%)	-
Neutrophil count 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%)	-	-
Insomnia	11 (21%)	-	-
Myalgia	10 (19%)	-	-
Abdominal pain	10 (19%)	-	-
Dyspnea	10 (19%)	-	-
Headache	8 (15%)	1 (2%)	-
Dizziness	9 (17%)	-	-
AST increased	9 (17%)	-	-

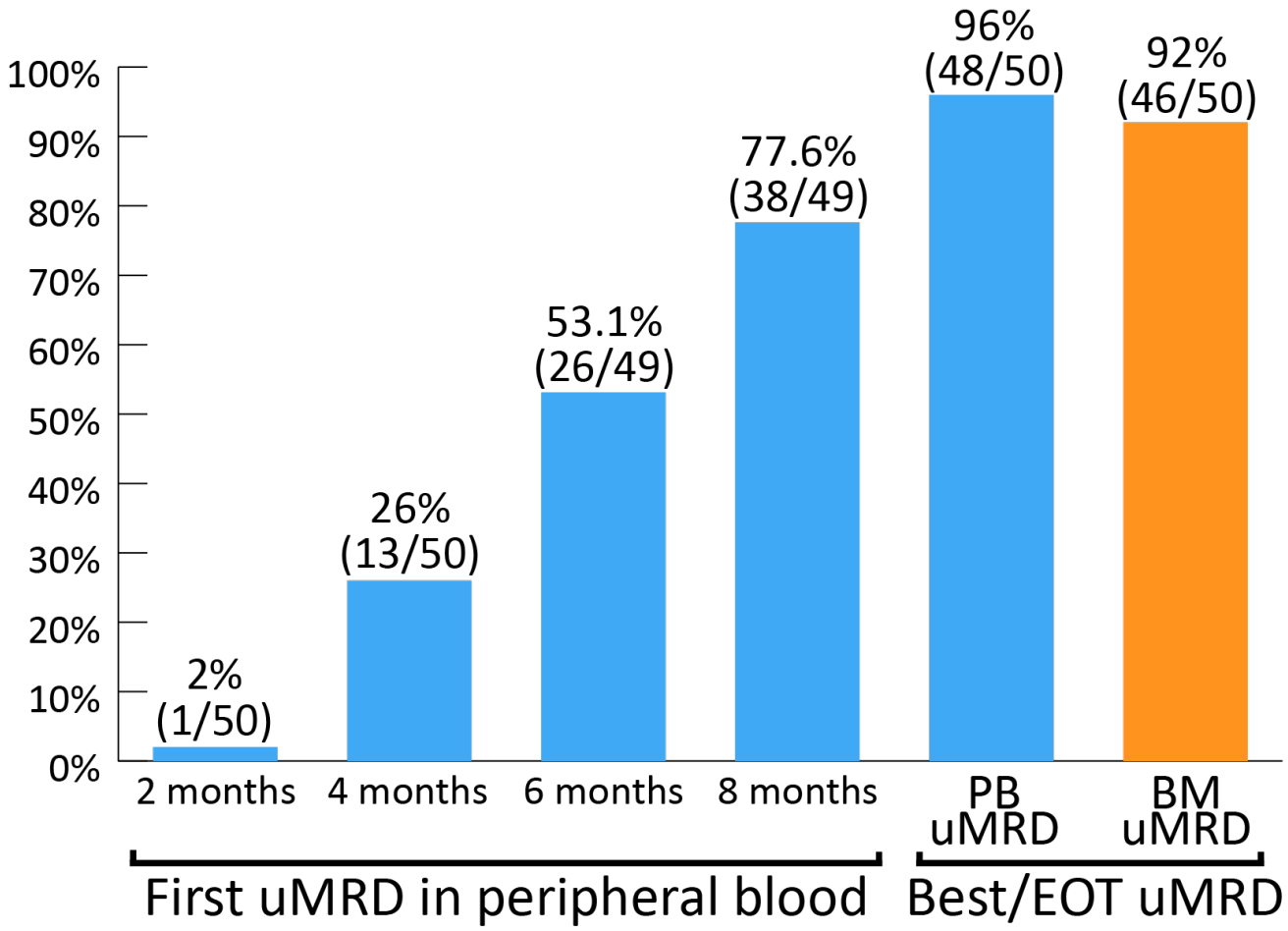
- No laboratory or clinical tumor lysis syndrome (Howard criteria)

Any grade AEs in ≥10% pts	Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)
Sinusitis	9 (17%)	-	-
ALK phosphatase increased	7 (13%)	1 (2%)	-
Anxiety	8 (15%)	-	-
Sore throat	8 (15%)	-	-
Hypocalcemia	8 (15%)	-	-
Dry skin	7 (13%)	-	-
Postnasal drip	7 (13%)	-	-
Back pain	7 (13%)	-	-
Weight loss	7 (13%)	-	-
Edema, limbs	6 (12%)	-	-
Non-cardiac chest pain	6 (12%)	-	-
Hypertension	6 (12%)	-	-

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).

MRD outcomes



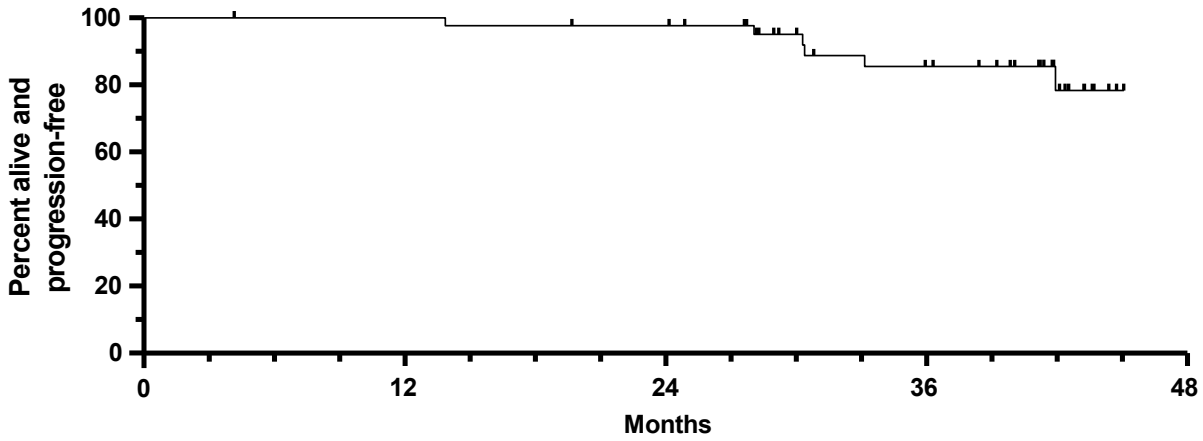
- 96% (48/50) uMRD in PB
- 92% (46/50) uMRD in both PB and BM
  - All met prespecified MRD endpoint/ treatment discontinuation criterion and stopped therapy after median of 10 mo (IQR 8-12 mo)

** uMRD = MRD $<10^{-4}$ (14-color flow cytometry)
LOD: 10^{-4}
Cutoff: uMRD if $<10^{-4}$

* One patient, initially ascertained as uMRD in peripheral blood at 8 mo, had subsequent serial testing which confirmed MRD positivity at the threshold of detection, so the patient was excluded from the proportion of patients achieving uMRD

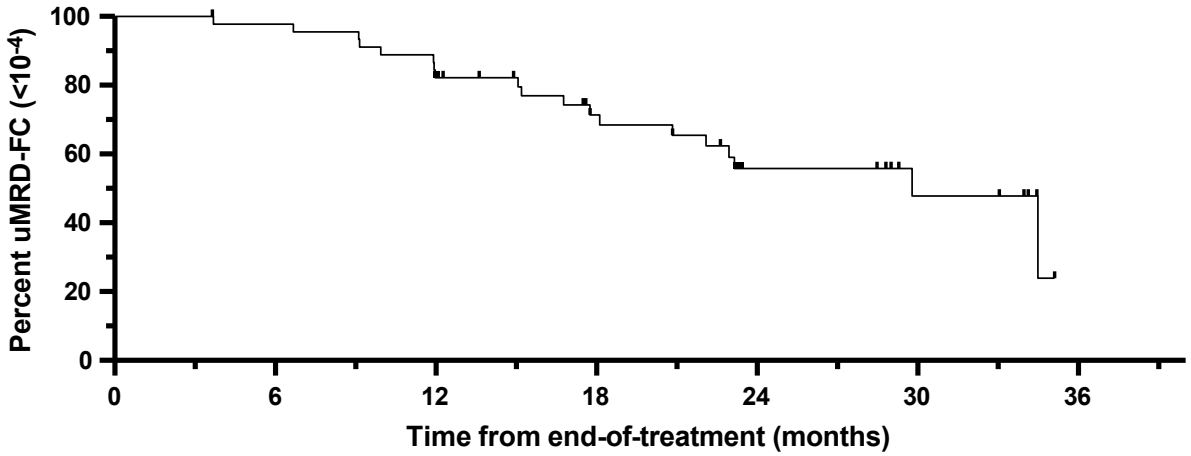
BOVen with uMRD-directed treatment duration resulted in durable PFS and uMRD

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 $\geq 10^{-4}$ or last confirmed uMRD $<10^{-4}$ (flow)

PFS, progression-free survival; uMRD-FC, undetectable MRD at $<10^{-4}$ by flow cytometry; EOT, End-of-Treatment; PB, peripheral blood

ΔMRD400 at Cycle 5 Day 1 predicted early uMRD in the bone marrow and shorter duration of therapy

- ΔMRD is decrease in PB MRD (Immunosequencing) at C5D1 (1 mo of Ven at target dose)
- 400-fold reduction optimal cutoff for predicting uMRD at $<10^{-4}$ within 8 mo (Youden Index)

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 or IGHV)

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

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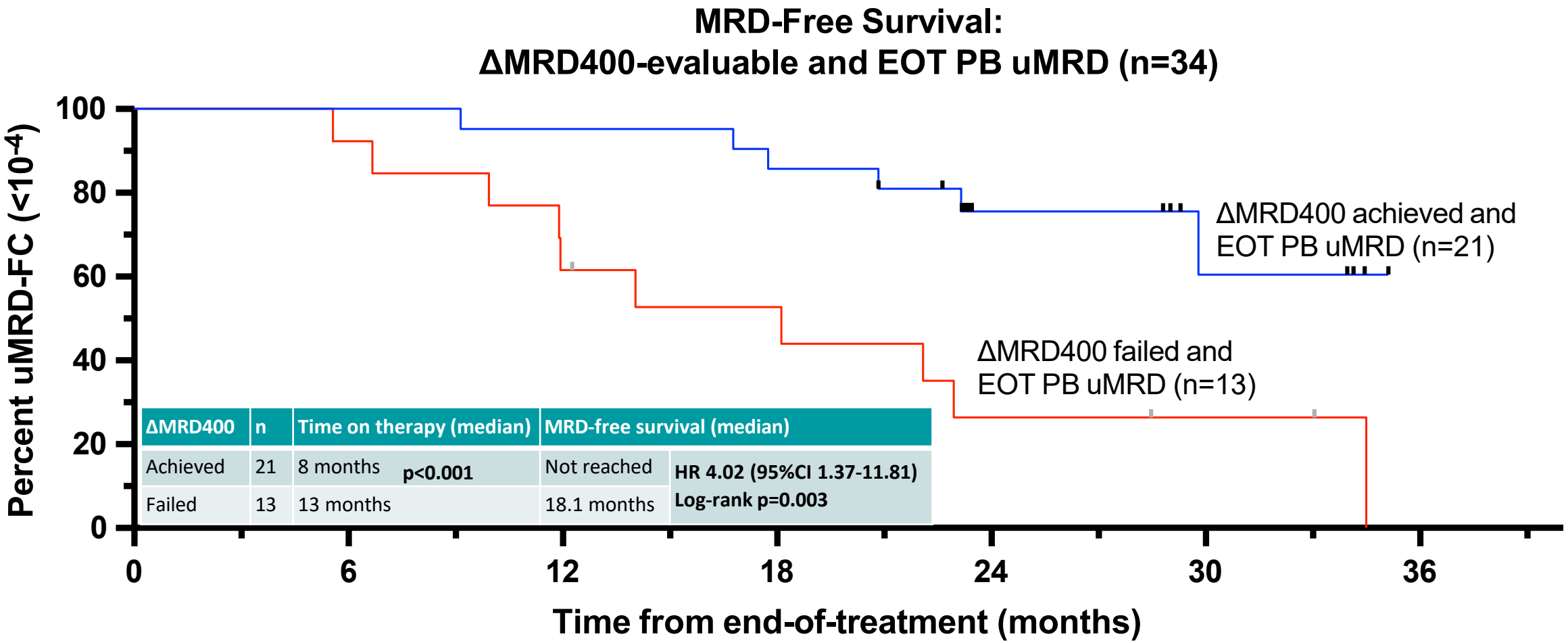
ΔMRD400 was associated with longer MRD-free survival despite shorter time on therapy



HR, hazard ratio; EOT, End-of-Treatment; PB, peripheral blood; uMRD, undetectable MRD

Conclusions

- BOVen was well tolerated with no additional safety signals with long-term follow-up
- BOVen achieved frequent uMRD ($<10^{-4}$) in peripheral blood (96%) and bone marrow (92%)
- Median duration of therapy was 10 months (IQR 8-12) including 2-month lead-in
- Long-term follow-up with durable progression-free survival
- MRD-free survival ($<10^{-4}$) was 29.8 months
  - MRD-free survival was 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)
- **Next:** 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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