A Phase 1/2 Study of Umbralisib, Ublituximab, and Venetoclax in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

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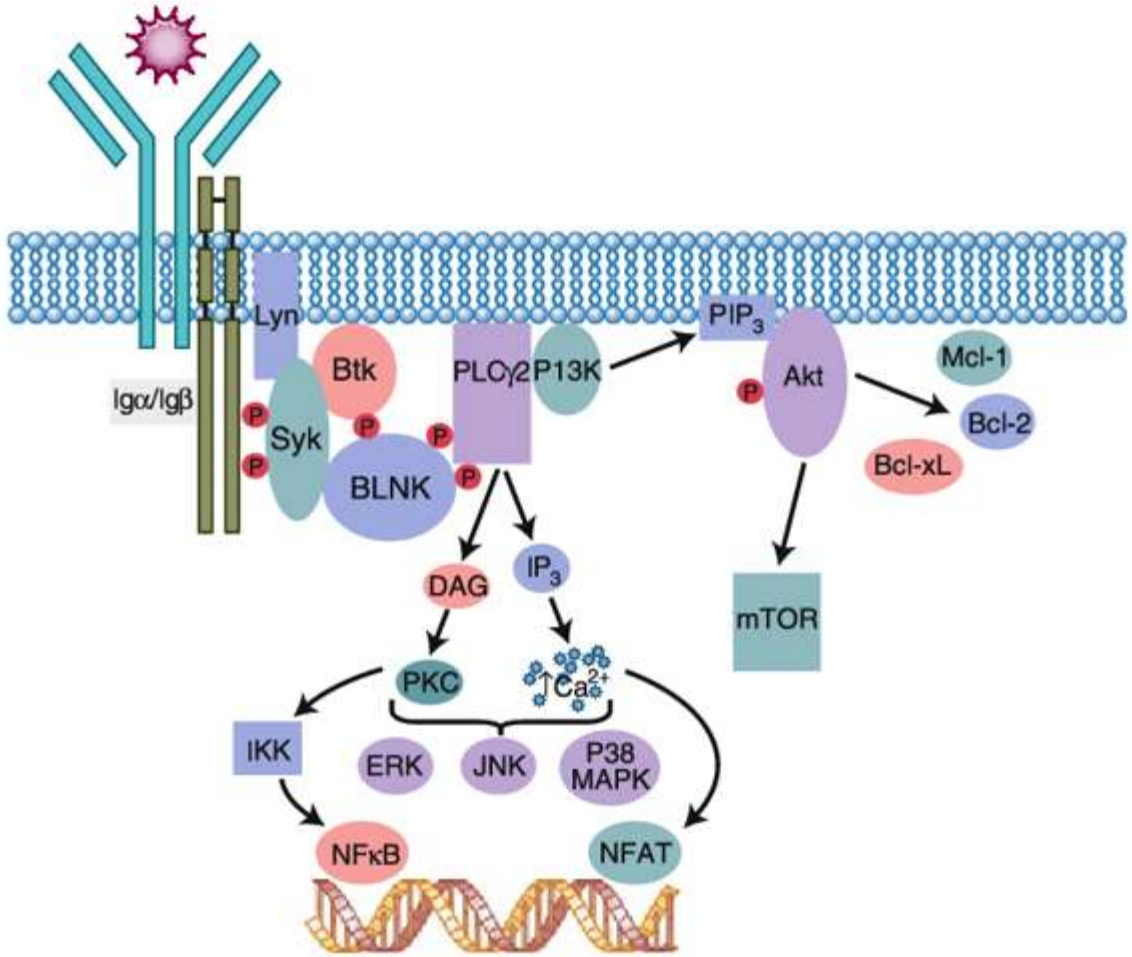
Disclosures

- Consulting and research support from TG Therapeutics

Background / Rationale

- Inhibition of BCR signaling and BCL2 is synergistic *in vitro*
- Targeting PI3K may prevent drug resistance to BCL2 inhibition
- Phase 1/2 study evaluating U2-Ven combination in a multicenter setting
  - Umbralisib and ublituximab (U2) combination ideal to minimize TLS risk
  - Goal is to achieve undetectable MRD in relapsed refractory CLL patients

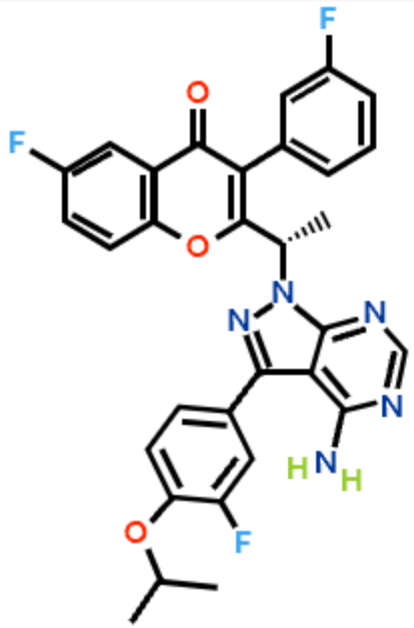
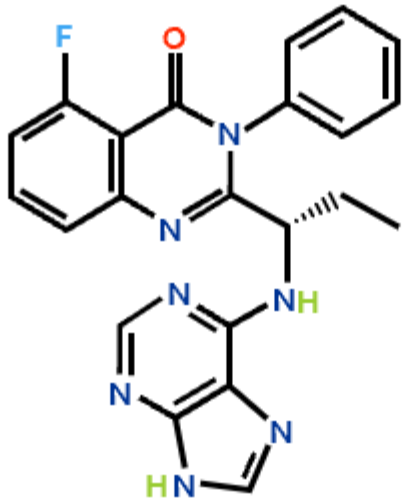
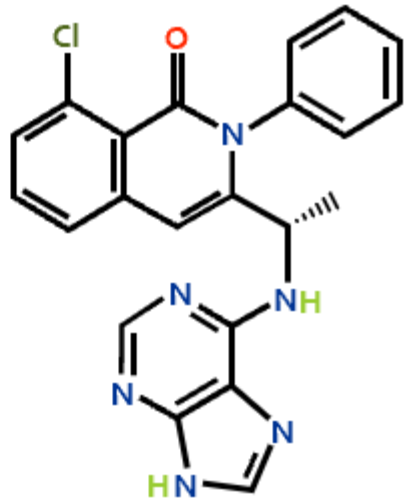


Cervantes-Gomez F et al. *Cancer Res.* 2015;21:3705-3715
Choudhary et al. *Cell Death Dis* 2015 Jan 15;6:e1593

Figure adapted from Riches et al., 2011

Background / Rationale: Umbralisib + Ublituximab (U2)

- Umbralisib is an oral, once-daily, novel, inhibitor of PI3Kδ and CK1ε
  - Preclinical: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib[2]
  - Clinical: Integrated analysis of long-term safety demonstrates low rates of immune-mediated toxicity[3]
- Ublituximab is a glycoengineered anti-CD20 monoclonal antibody
  - Enhanced ADCC compared to rituximab
- UNITY-CLL study with U2 in treatment-naïve and previously treated CLL recently met its primary endpoint of PFS

Umbralisib[1]	Idelalisib[1]	Duvelisib[1]
		

Isoform	K_d (nM)		
PI3kα	>10000	600	40
PI3Kβ	>10000	19	0.89
PI3Kγ	1400	9.1	0.21
PI3Kδ	6.2	1.2	0.047
CK1ε	180	>30,000	>30,000

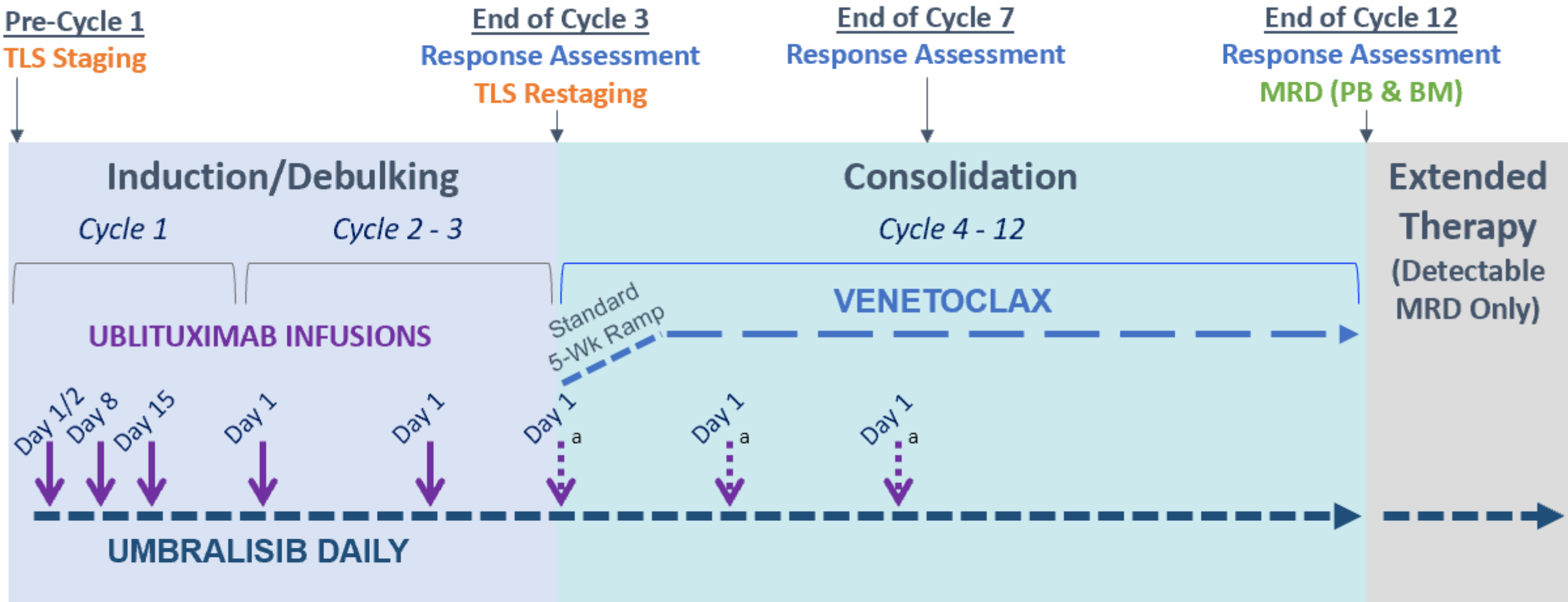
[1]Burris et al., Lancet Oncology 2018; [2]Maharaj et al.,Blood Advances, 2020; [3]Davids et al. (PF444), EHA 2018

Study Design and Objectives

- **Study Design**
  - Multi-center Phase 1/2 dose-escalation (3+3 design) study to assess the safety & efficacy of U2+venetoclax in patients with R/R CLL
    - Fixed dose ublituximab (900 mg), escalating doses of umbralisib (600 mg and 800 mg)
    - Standard dosing of venetoclax (5-week ramp up to 400 mg)
- **Primary objective**
  - To evaluate the safety of venetoclax addition after U2 induction
- **Secondary objectives**
  - Clinical efficacy as defined by CR rate and PFS (iwCLL 2018)
  - Undetectable MRD rate after 12 cycles of therapy
    - Centrally conducted 8-color flow cytometry

CR: complete response; PFS: progression-free survival; uMRD: undetectable minimal residual disease.

Study Design: Treatment Schedule



- [a]Protocol amended June 11th 2019 to add ublituximab infusions (900 mg) on Day 1 of Cycles 4, 5, and 6
- MRD measured by flow cytometry

Cycle = 28 Days

Key Eligibility Criteria

- CLL/SLL: progressed after at least one prior therapy and requiring treatment
  - Mid-study amendment required CLL pts to be BTKi intolerant or refractory (PD within 6 mos of prior BTK)
- 21-day washout from prior therapy except prior BTK inhibitor (longer of 3 days or 5 half-lives)
- ANC >750/µL, platelet count >40,000/µL
- CrCl >50 mL/min for Phase 1 and >30 mL/min for Phase 2
- Prior exposure to BCL2 or PI3K inhibitor was NOT an exclusion

Baseline Characteristics

Evaluable for Safety, n	47
Evaluable for Efficacy, n	46†
Median Age, years (range)	64 (43 - 85)
Male/Female, n	33 / 14
ECOG, 0/1/2, n	6 / 39 / 2
Prior Therapy Regimens, median (range)	2 (1 – 6)
Refractory to immediate prior therapy, n (%)	18 (38%)
Prior anti-CD20, n (%)	40 (85%)
Prior chemoimmunotherapy, n (%)	34 (72%)
Prior BTKi (ibrutinib / acalabrutinib), n (%)	27 (57%)
Refractory to prior BTKi, % (n/N)	48% (13/27)
BTK or PLCγ mutation detected, % (n/N)	73% (11/15)*
Prior PI3Ki, n (%)	3 (6%)
Prior venetoclax, n (%)	1 (2%)

Molecular Aberrations

High Risk Features:	n/N (%)
11q deletion	10/46 (22%)
17p deletion	10/46 (22%)
TP53 mutation	10/33 (30%)
NOTCH1 mutation	8/27 (30%)
SF3B1 mutation	5/27 (19%)
IGHV unmutated	29/39 (74%)
At least 1 high risk feature	**34/47 (72%)**

† 1 patient not evaluable
– discontinued prior to first response assessment and did not receive venetoclax

*15 patients tested for mutations

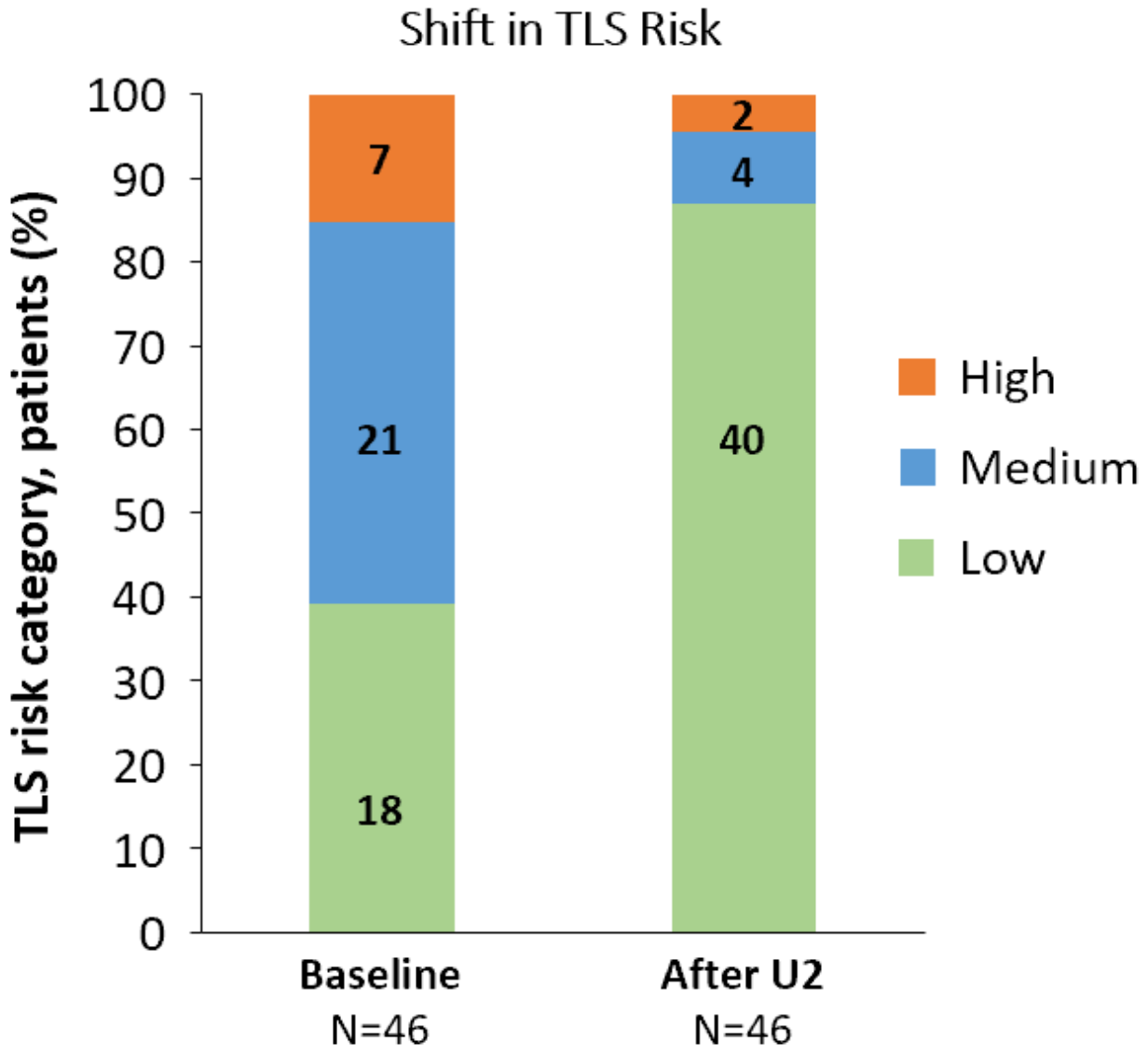
Adverse Events (All Causality) >20% (N=47)

	All Grades		Grade 3/4	
	N	%	N	%
Infusion reaction	30	64%	4	9%
Neutropenia	25	53%	13	28%
Leukopenia	25	53%	7	15%
Thrombocytopenia	24	51%		
Anemia	23	49%	3	6%
Creatinine increase	22	47%		
Lymphocytopenia	20	43%	7	15%
Diarrhea	18	38%	4	9%
Nausea	16	34%		
AST increase	14	30%	1	2%
Fatigue	14	30%		
Alkaline phos increase	12	26%		
ALT increase	10	21%	1	2%

- G3/4 AEs of Special Interest:
  - Pneumonia: 3 (6%)
  - Colitis: 2 (4%) – 1 of whom had c-diff
  - TLS: 1 (2%) - ublituximab related, prior to ven
  - Rash: 1 (2%)
  - Pneumonitis: 0
  - LFT elevations: 1 (2%)
- Dose of umbralisib was reduced in 3 (6%) patients
- Two (4%) patients discontinued all therapy due to AEs related to therapy:
  - Diarrhea (Grade 3)
    - Patient off all therapy at Cycle 9 but still achieved uMRD in PB and BM at Cycle 12
  - Rash (Grade 1)

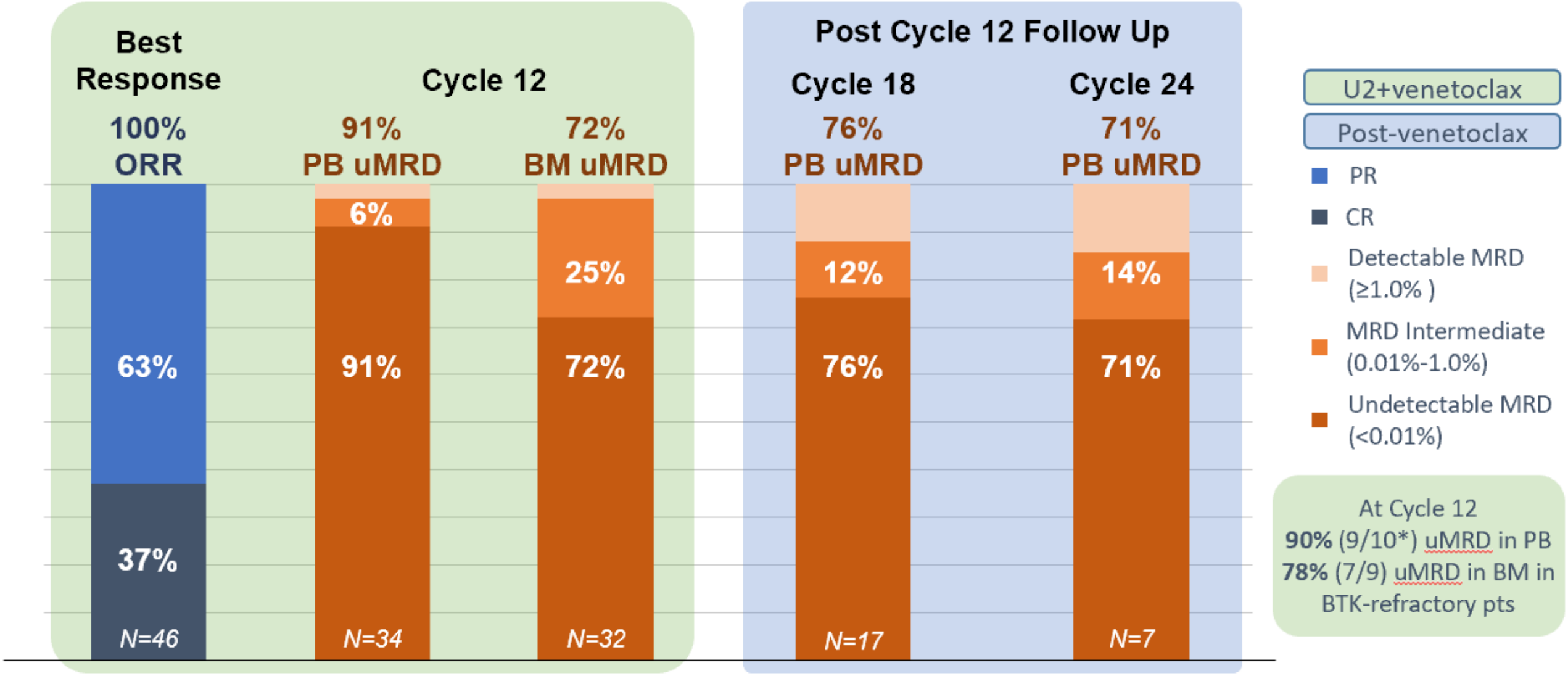
uMRD: undetectable minimal residual disease; BM: bone marrow; PB: peripheral blood.

3 Cycles of U2 Induction Reduces Venetoclax TLS risk



- After 3 cycles of ublituximab and umbralisib debulking:
  - 79% relative reduction in TLS risk after 3 cycles of U2
  - No patients developed clinical or laboratory TLS during venetoclax ramp up

Efficacy: Response and MRD

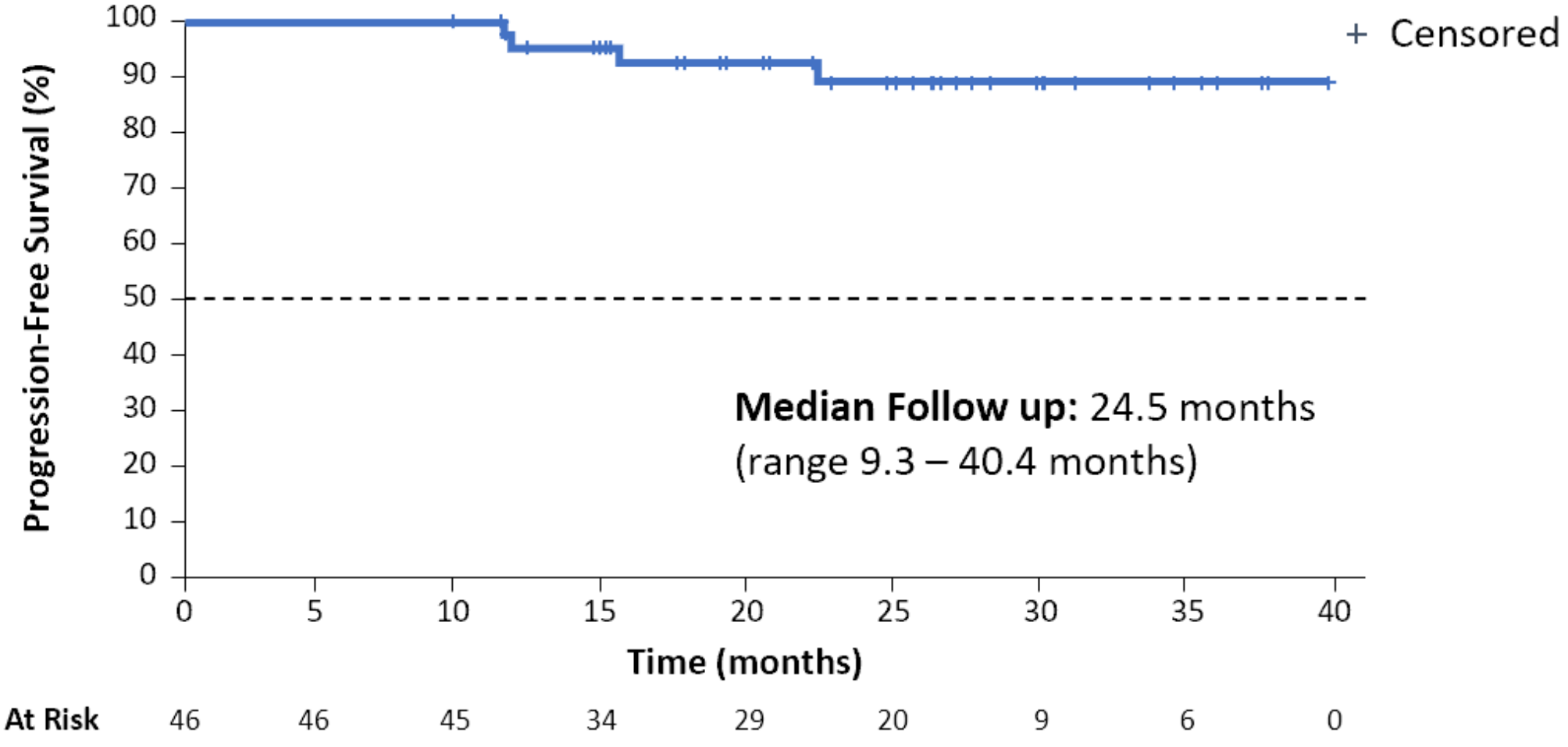


At Cycle 12
90% (9/10*) uMRD in PB
78% (7/9) uMRD in BM in BTK-refractory pts

BM: bone marrow; ORR: Overall response rate; PB: peripheral blood; uMRD: undetectable minimal residual disease.

*3 BTK Ref pts too early to evaluate

Efficacy: Progression-free survival (n=46)



1 death due to COVID, occurring 4 mos after Cycle 12 uMRD in BM, and discontinuation of all therapy

Conclusions

- Combination of umbralisib, ublituximab and venetoclax is well tolerated
  - U2 induction mitigates TLS risk
- Encouraging efficacy in relapsed/refractory CLL patients including those refractory to prior BTKi
  - 100% ORR, 37% CR rate
  - Undetectable MRD of 91% and 72% in peripheral blood and bone marrow, respectively, at Cycle 12
  - Over 70% of patients remain undetectable following completion of venetoclax
  - Re-treatment strategies are being investigated for patients that have progressed
- Expansion cohorts for Richter's transformation and mantle cell lymphoma are currently open for enrollment
- ULTRA-V: Phase 2/3 Study of U2-ven in treatment naïve and relapsed/refractory CLL is ongoing

Acknowledgments

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- Participating Centers:

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