

Phase I/II Study of Umbralisib in Combination with Ublituximab and Venetoclax (U2-Ven) in Patients with Relapsed/Refractory CLL

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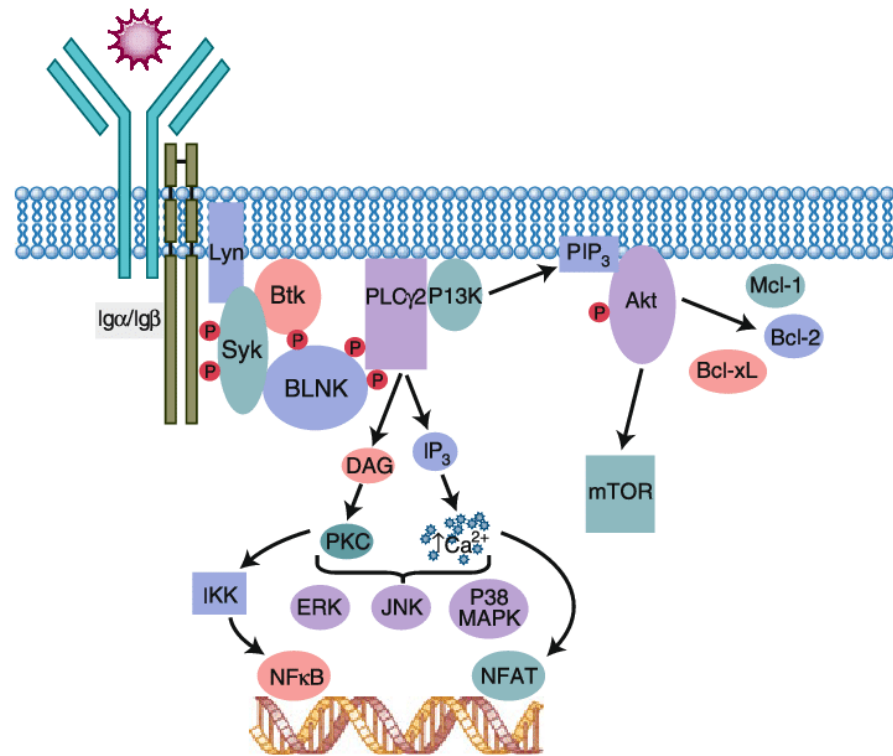
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Background / Rationale: Venetoclax

- Preclinical additive to synergistic cytotoxicity between inhibition of BCR signaling and BCL2
- Targeting PI3K may prevent drug resistance to BCL2 inhibition
- Phase 1/2 study evaluating U2-Ven combination in a multicenter setting
 - PI3K + CD20 inhibition ideal to minimize TLS risk for BTK inhibition failures
 - Achieve MRD negativity in relapsed refractory CLL patients

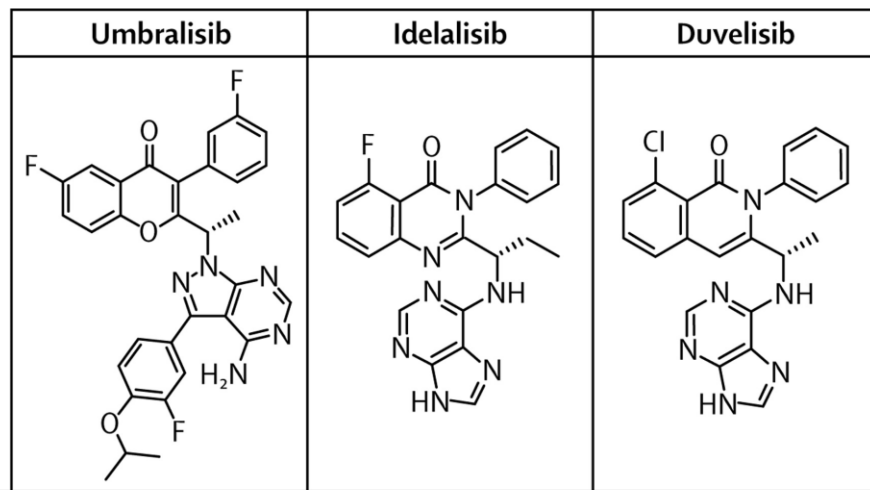


Cervantes-Gomez F et al. *Cancer Res.* 2015;21:3705-3715
Choudhary et al. *Cell Death Dis* 2015 Jan 15;6:e1593

Figure adapted from Riches et al., 2011

Background / Rationale: Umbralisib + Ublituximab (U2)

- Umbralisib: novel PI3K δ /CK1 ϵ dual inhibitor, with a unique structure and improved tolerability¹
 - Preclinical: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib²
 - Clinical: Integrated analysis of long-term safety: demonstrates low rates of immune-mediated toxicity³
- Ublituximab: glycoengineered anti-CD20 monoclonal antibody
 - Enhanced ADCC compared to rituximab
- U2: Phase 1 trial⁴
 - Low rates of immune mediated AEs
 - 62% ORR and median PFS of 28 months



Isoform	K _d (nM)		
PI3K α	>10 000	600	40
PI3K β	>10 000	19	0.89
PI3K γ	1400	9.1	0.21
PI3K δ	6.2	1.2	0.047
CK1 ϵ	180	>30 000	>30 000

¹Burris et al., Lancet Oncology 2018; ²Maharaj et al., ASH 2017;

³Dauids et al., EHA 2018; ⁴Unning et al., Blood 2019

Study Design and Objectives

■ Study Design

- Multi-center Phase I/II 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)

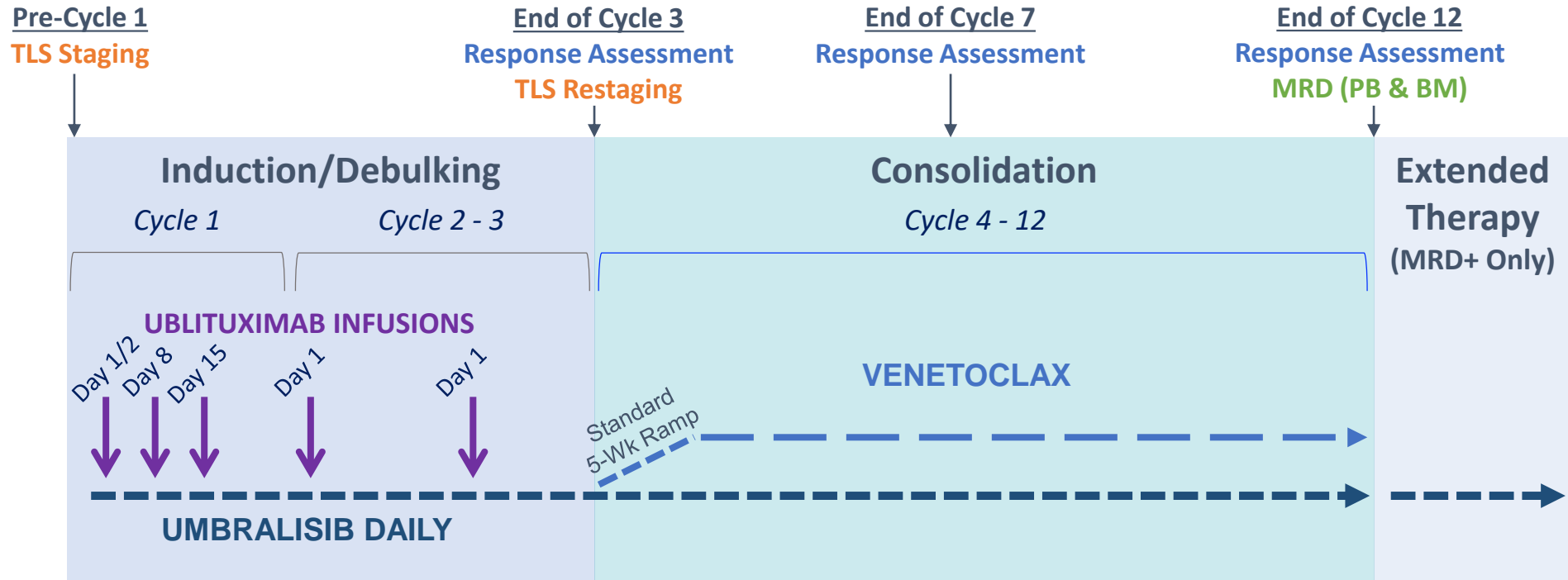
■ Primary objective

- To evaluate the safety of venetoclax addition after U2 induction

■ Secondary objectives

- Clinical efficacy as defined by CR rate and PFS (iwCLL 2018)
- MRD negativity rate after 12 cycles of therapy
 - Centrally conducted 8-color flow cytometry

Study Design: Treatment Schedule



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/ μ L, platelet count > 40,000/ μ L
- CrCl > 50 mL/min for Phase I and > 30 mL/min for Phase II
- Prior exposure to BCL2 or PI3K inhibitor was NOT an exclusion

Baseline Characteristics

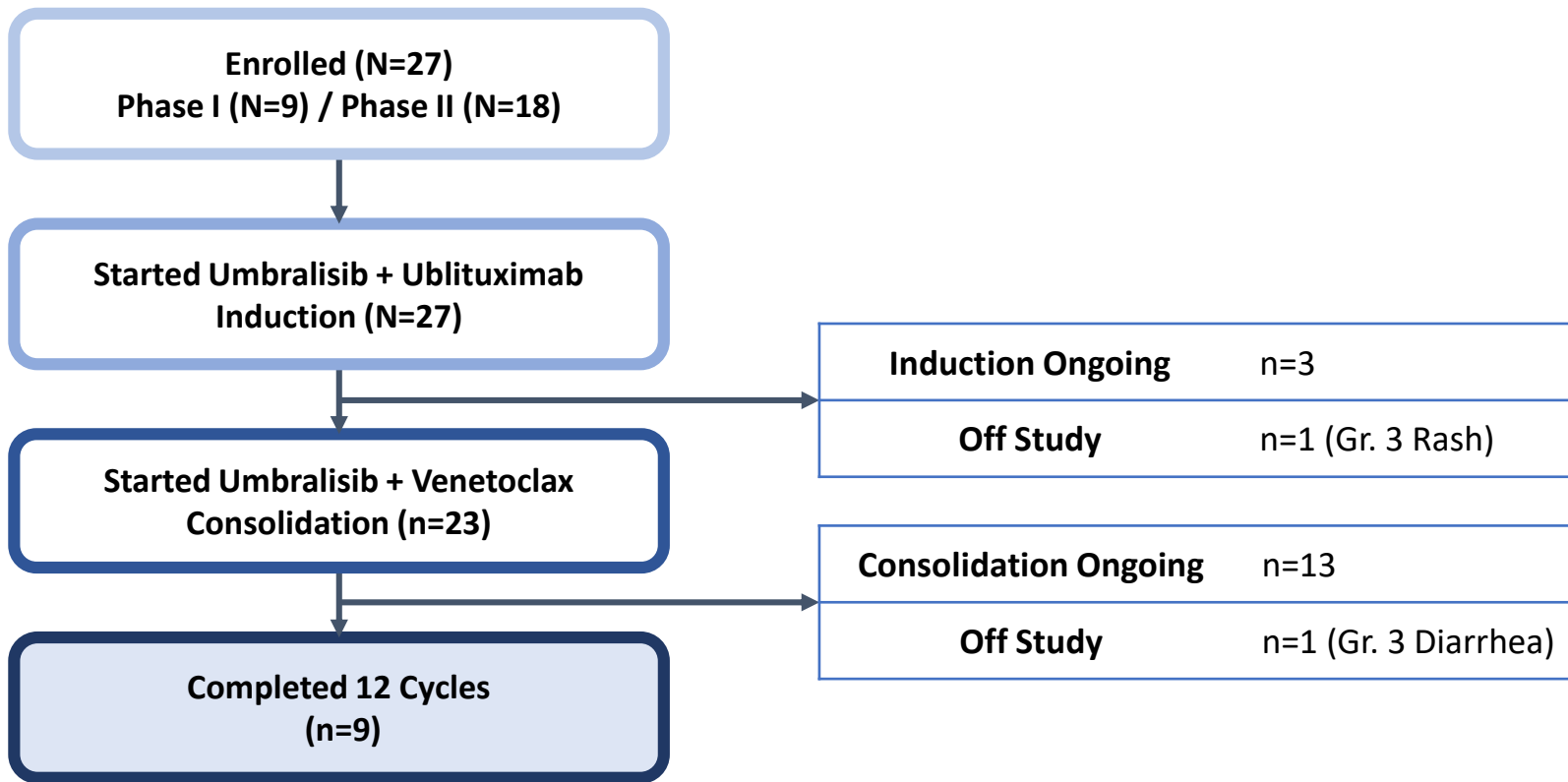
Evaluable for Safety, n	27
Evaluable for Efficacy, n	23 [†]
Median Age, years (range)	63 (43 - 83)
Male/Female	18 / 9
ECOG, 0/1/2	3 / 22 / 2
Median Creatinine Clearance, mL/min (range)	75 (45-135)
Prior Therapy Regimens, median (range)	1 (1 – 5)
Refractory to immediate prior therapy, n (%)	7 (26%)
Prior anti-CD20, n (%)	21 (78%)
Prior chemoimmunotherapy, n (%)	18 (67%)
Prior BTKi (ibrutinib / acalabrutinib), n (%)	13 (48%)
Refractory to prior BTK	7/13 (54%)
BTK or PLCγ mutation detected	5/7 (71%)
Prior PI3Ki, n (%)	2 (7%)
Prior venetoclax, n (%)	1 (4%)

Molecular Aberrations

At least 1 high risk feature (del17p, del11q, TP53mut, NOTCH1mut)	14 (52%)
11q deletion, n (%)	6/27
17p del/TP53 mutation, n (%)	5/27
NOTCH1 mutation, n (%)	5/17
SF3B1 mutation, n (%)	1/17
IGHV unmutated, n (%)	13/21

[†]3 patients too early to evaluate;
1 patient off study prior to first response assessment

Overall Disposition



Disposition

Enrollment by Cohort

Cohort	Umbralisib Dose	n
Dose level 1	600 mg	3
Dose level 2	800 mg	6
Phase II	800 mg	18

Dose Modifications

Agent	Reduction (n)	Withdrawn (n)
Ublituximab	0	2
Umbralisib	1	2
Venetoclax	1	1

- DLT period: cycles 4 and 5
 - 1 DLT at 800 mg
 - Lower GI bleed, Cycle 5 (not related)
 - Resolved in 3 days
- MTD not reached

Adverse Events (All Causality) >15% (N=27)

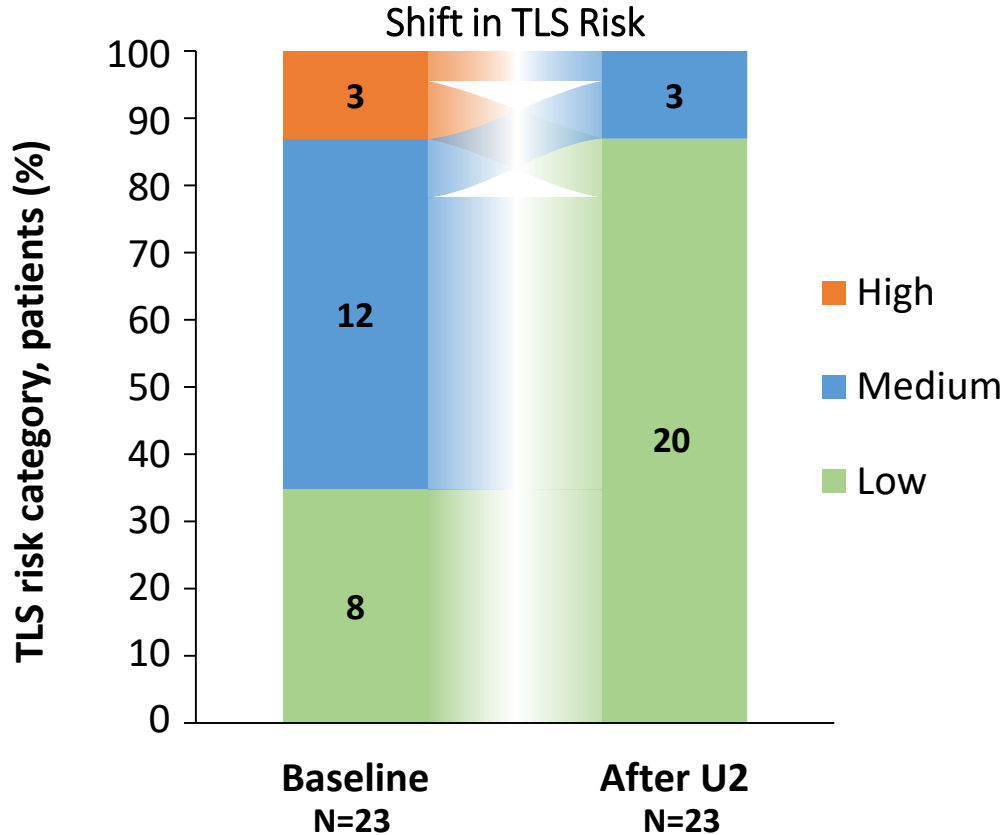
	All Grades		Grade 3/4	
	N	%	N	%
Infusion reaction	18	67%	2	7%
Neutropenia	15	56%	5	19%
Leukopenia	13	48%	4	15%
Creatinine increase	13	48%	-	-
Thrombocytopenia	13	48%	-	-
Anemia	12	44%	1	4%
Nausea	10	37%	-	-
AST increase	10	37%	-	-
Diarrhea	9	33%	1	4%
Alkaline phos increase	8	30%	-	-
Fatigue	8	30%	-	-
ALT increase	7	26%	-	-
Hypocalcemia	7	26%	-	-
Rash	7	26%	1	4%
Hyperkalemia	5	19%	-	-

- Additional Grade 3/4 AEs:
 - DVT (2)
 - Lower GI bleed (1)
 - Supraventricular tachycardia (1)
 - Anxiety (1)
 - Hypophosphatemia (1)
 - Dyspnea (1)

- No TLS or lab tumor lysis

- No grade 3/4 LFT elevations

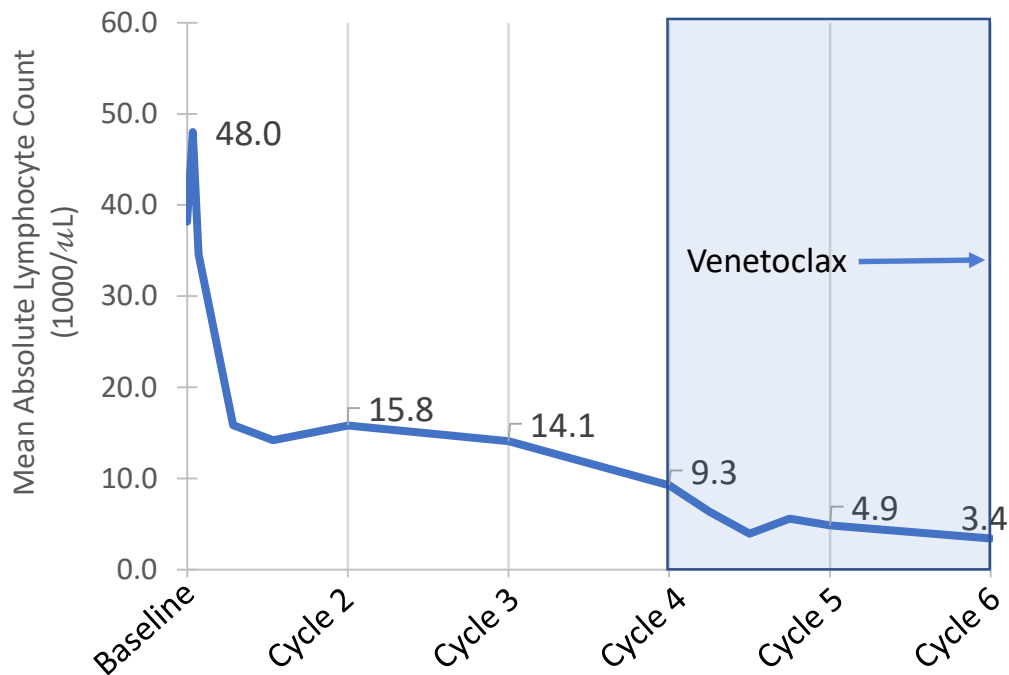
3 Cycles of U2 Induction Reduces Venetoclax TLS risk



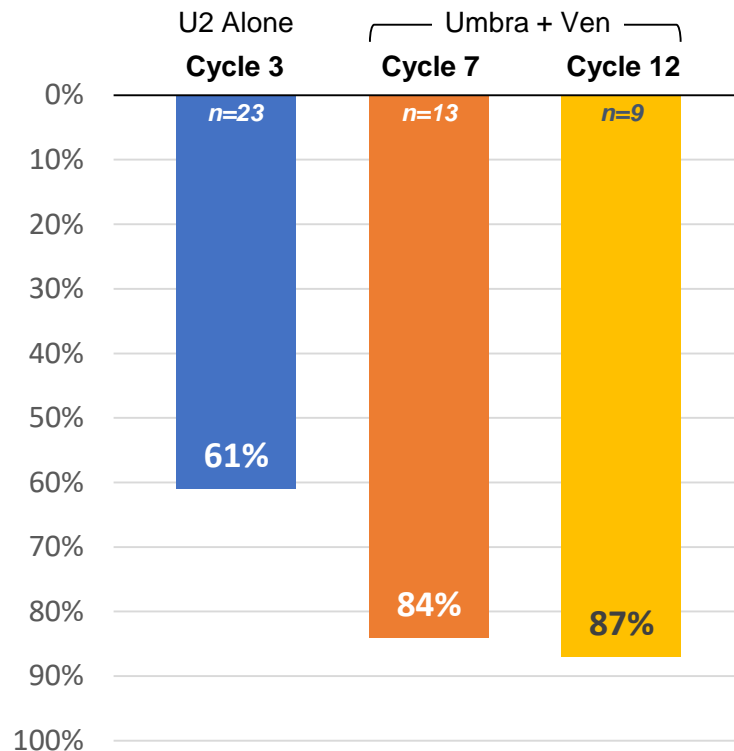
- After 3 cycles of ublituximab and umbralisib debulking:
 - No TLS High-Risk patients remaining
 - No patients developed clinical or laboratory TLS during venetoclax ramp up

Efficacy

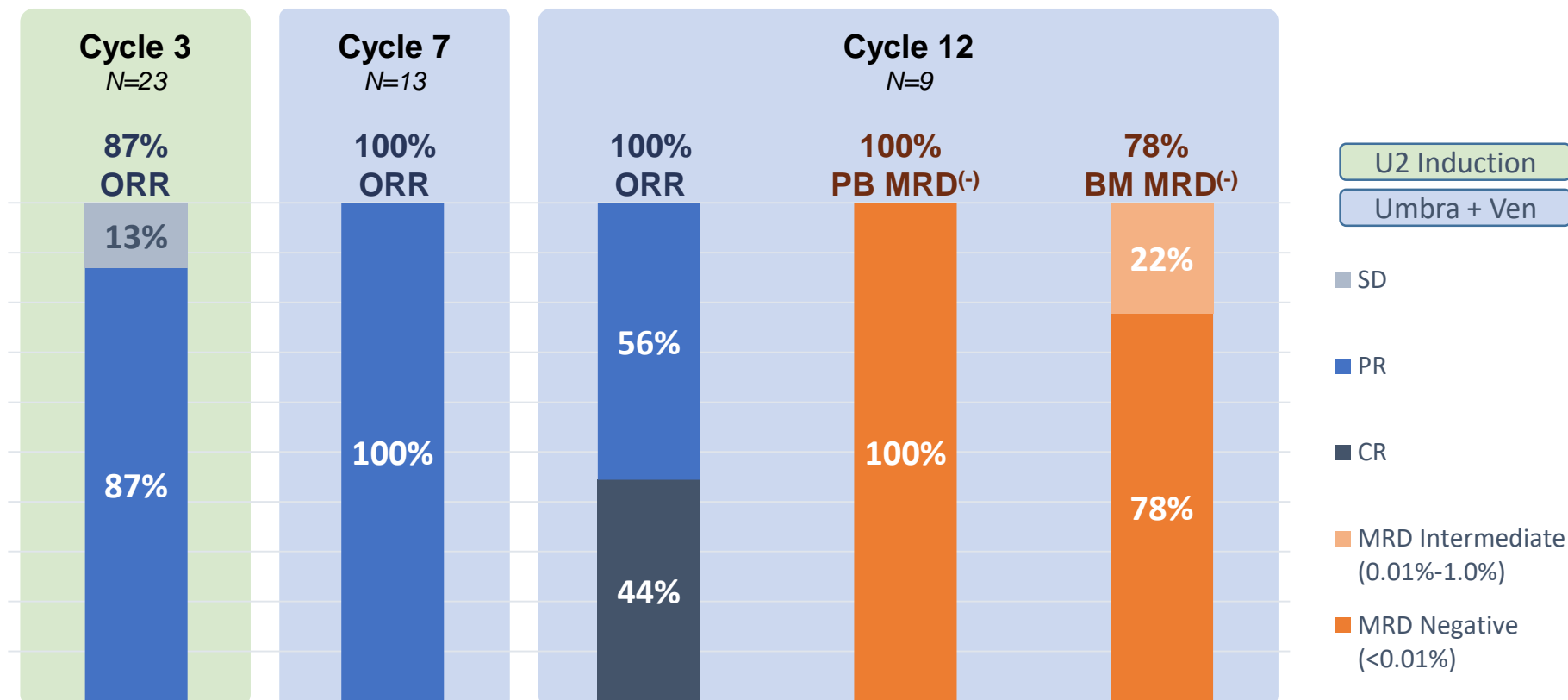
ALC Reduction Through Cycle 6



Mean % Lymph Node Reduction from Baseline

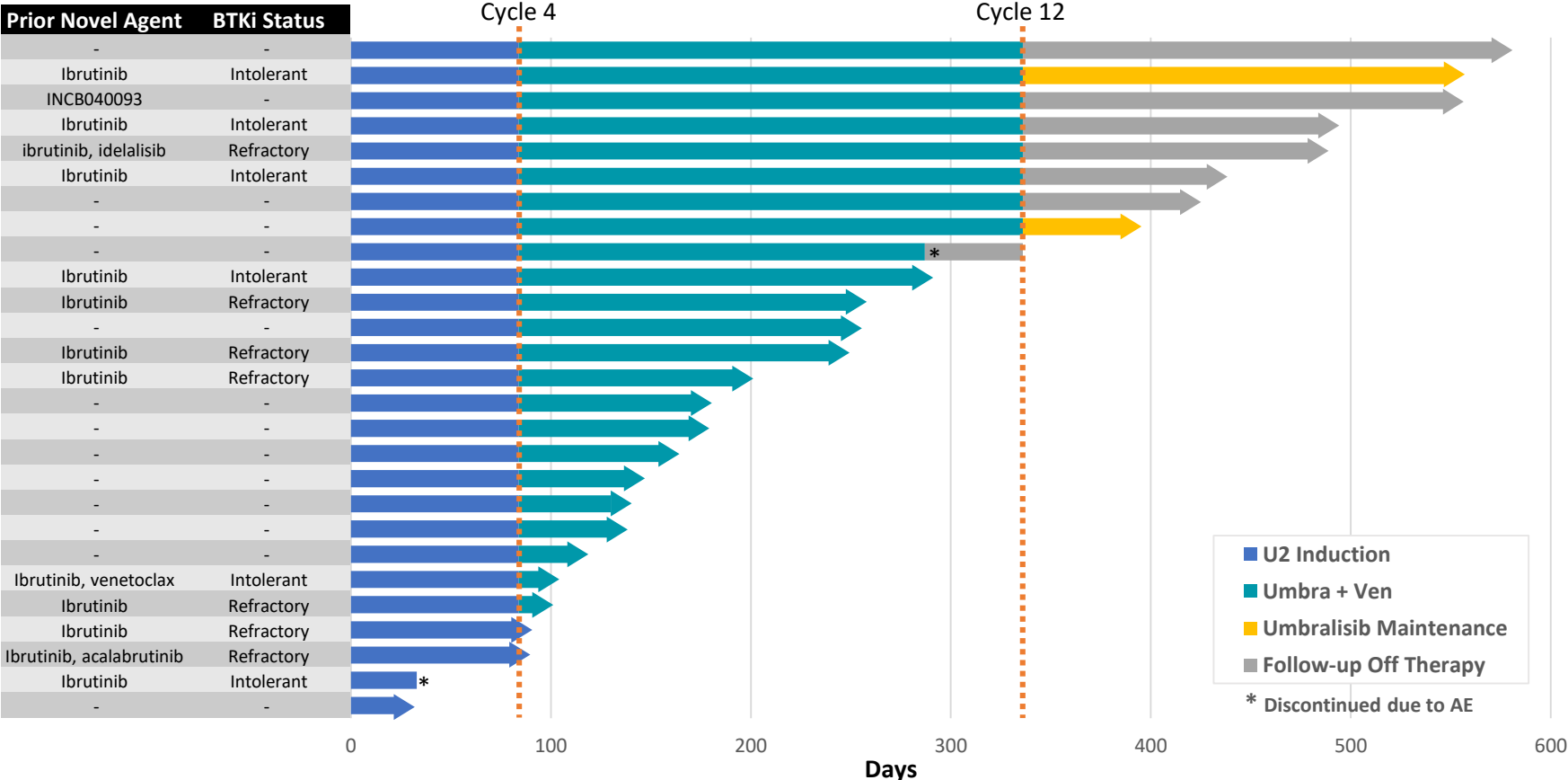


Efficacy: Response and MRD

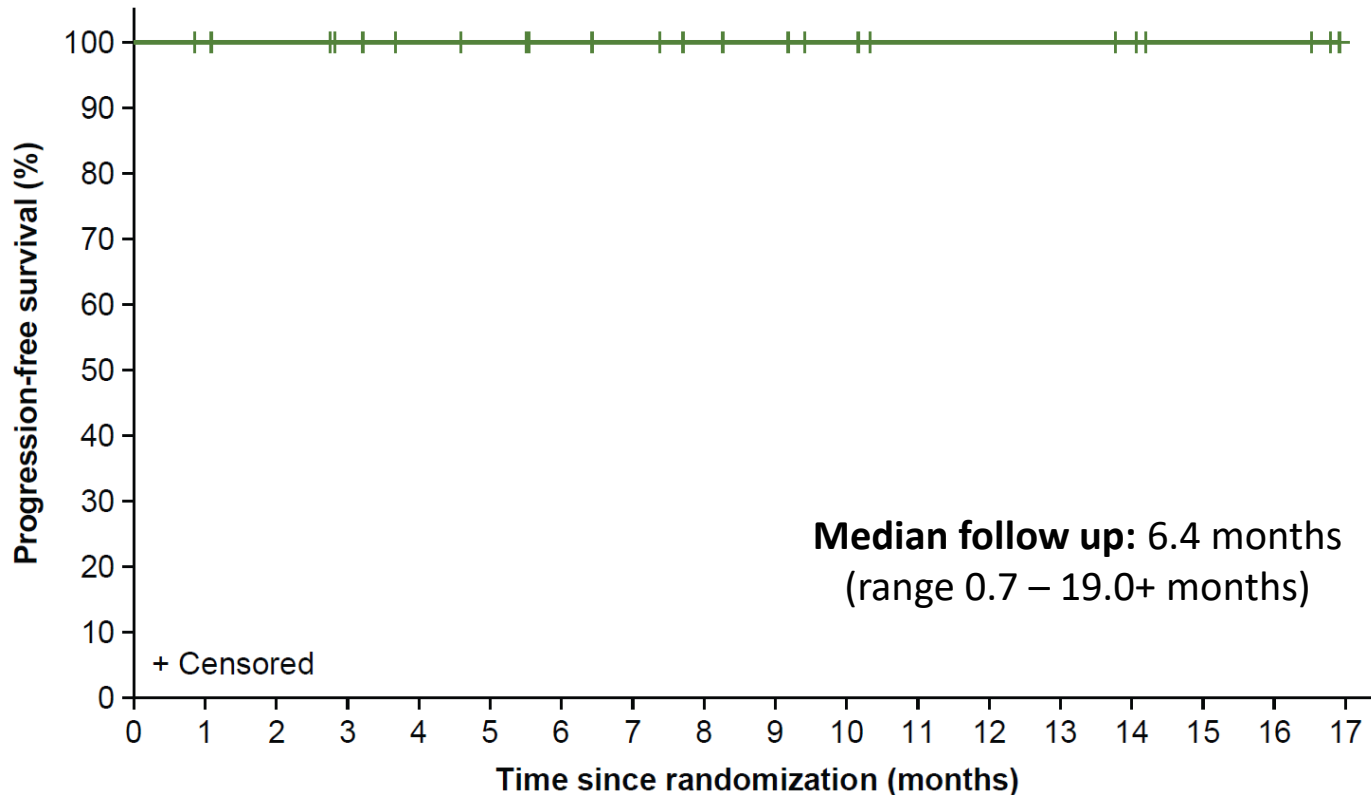


Cycle 3 & 7 Assessments were by CT only without BM, therefore CR could not be assessed

Efficacy & Tolerability: Duration of Exposure



Efficacy: Progression-free survival (n=27)



Conclusions

- Umbralisib, ublituximab and venetoclax is well tolerated at the Phase 2 doses
 - U2 induction mitigates TLS risk
 - Manageable myelosuppression and GI effects resulting in low rate (7%) of discontinuation due to AE
- Early evidence of MRD negativity with 12 cycles of therapy
 - 9/9 and 7/9 undetectable in peripheral blood and marrow respectively
- Relapsed/refractory CLL enrollment is ongoing in BTK inhibitor treated patients
 - Expansion cohorts for Richters transformation and mantle cell lymphoma
- ULTRA-V Phase 2 Study of U2-Ven regimen ongoing in treatment naïve and relapsed/refractory CLL

Acknowledgments

- Thank you to the patients and their families for their participation.

- Participating Centers:



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