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

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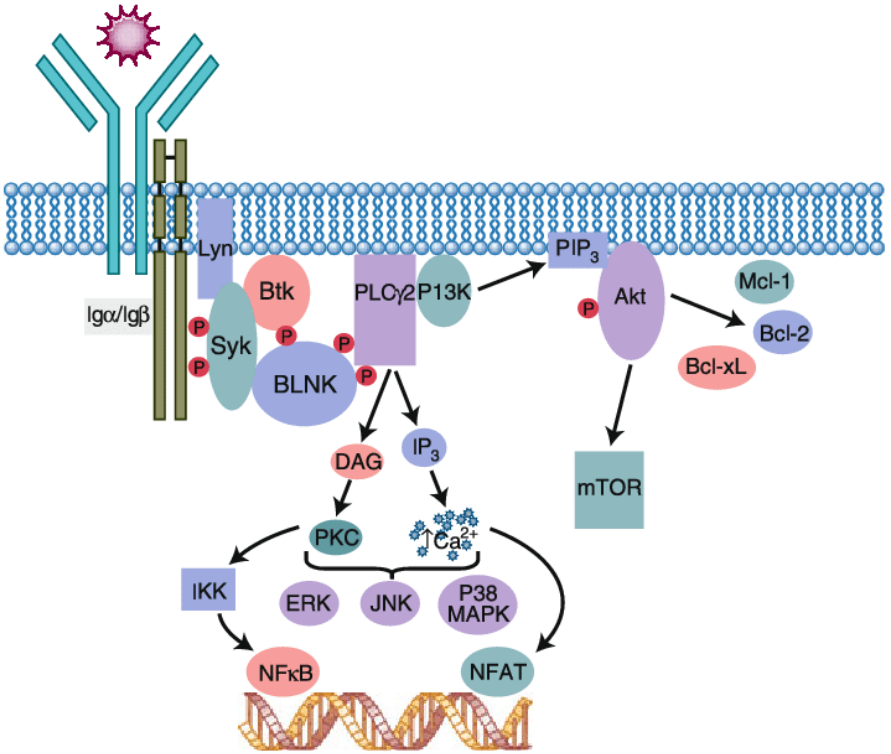
Background / Rationale: Venetoclax

- 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

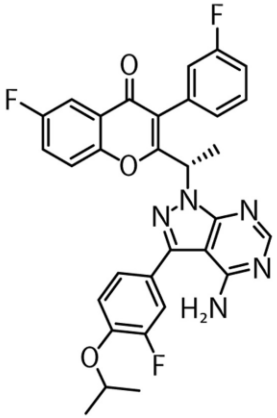
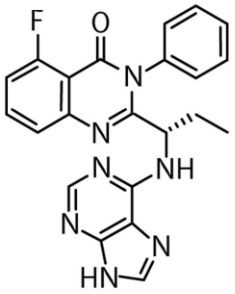
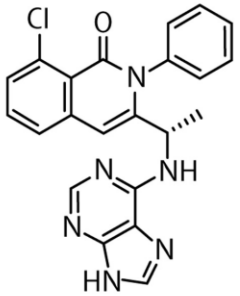


Cervantes-Gomez F et al. *Cancer Res.* 2015;21:3705-3715
Choudhary et al. *Cell Death Dis* 2015 Jan 15;6:e1593

Figure adapted from Riches et al., 2011

Background / Rationale: Umbralisib + Ublituximab (U2)

- Umbralisib: novel PI3Kδ/CK1ε dual inhibitor, with a unique structure and improved tolerability[1]
  - 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: glycoengineered anti-CD20 monoclonal antibody
  - Enhanced ADCC compared to rituximab
- U2: Phase 1 trial[4]
  - Low rates of immune mediated AEs
  - 62% ORR and median PFS of 28 months

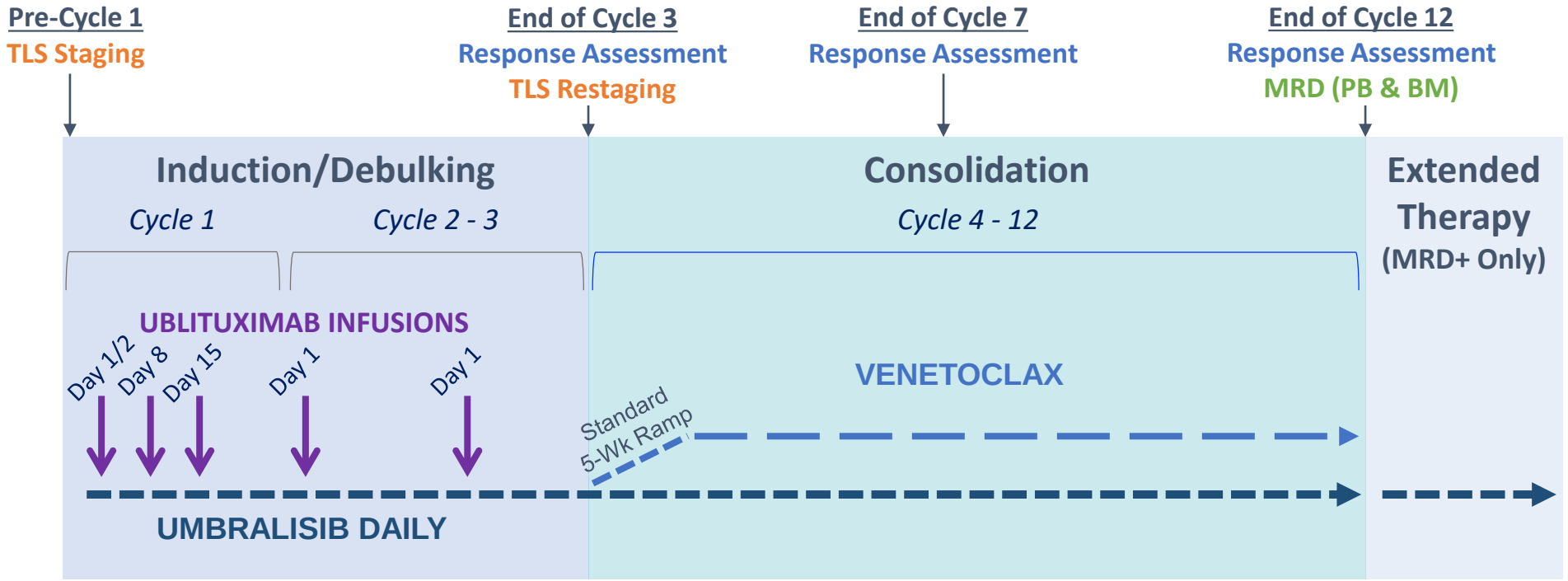
	Umbralisib	Idelalisib	Duvelisib
			
Isoform	**K_d (nM)**		
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047
CK1ε	180	>30 000	>30 000

[1]Burris et al., Lancet Oncology 2018; [2]Maharaj et al., ASH 2017; [3]Davids et al., EHA 2018; [4]Lunning 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



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 I and >30 mL/min for Phase II
- Prior exposure to BCL2 or PI3K inhibitor was NOT an exclusion

Baseline Characteristics

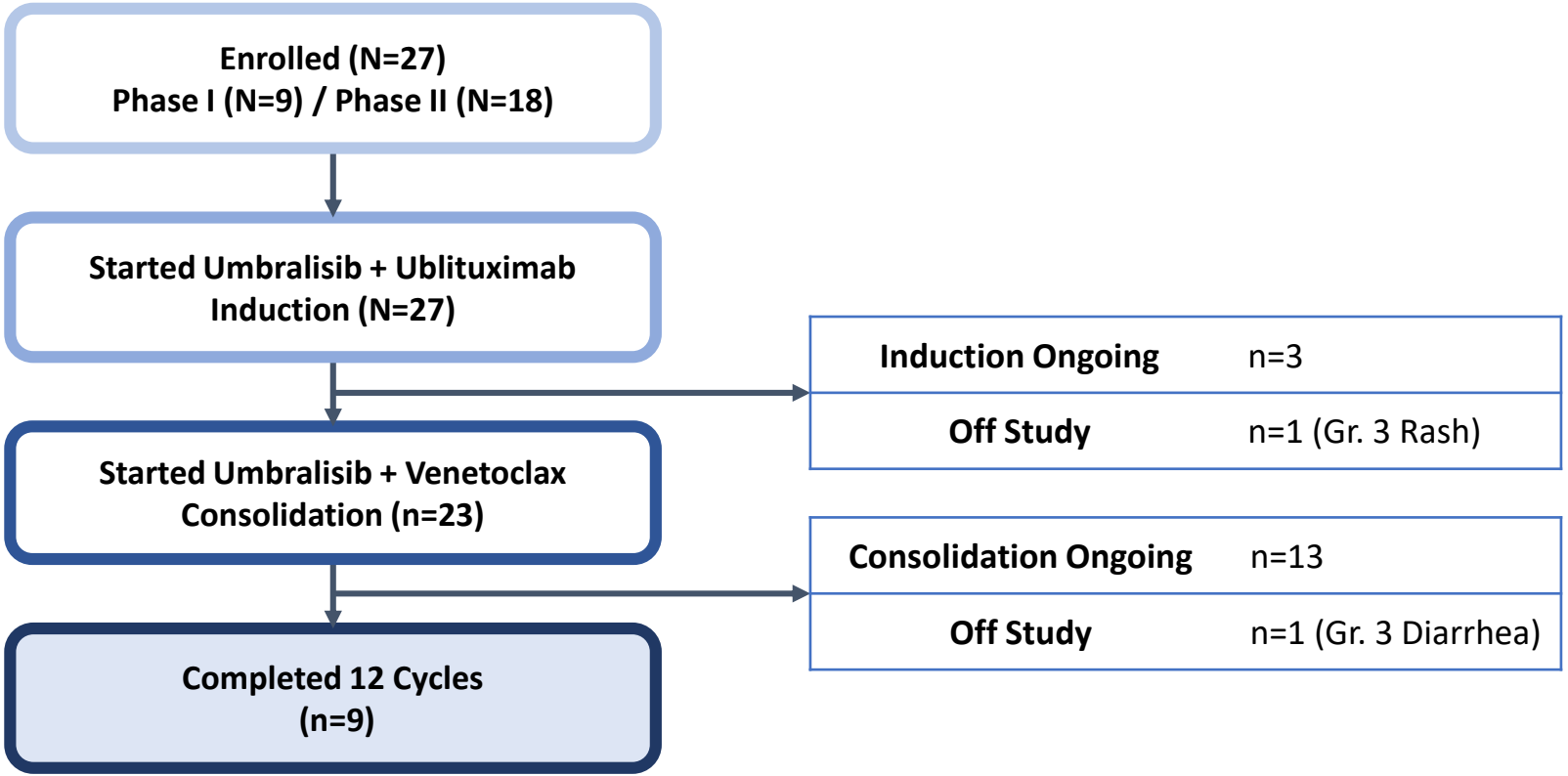
Evaluable for Safety, n	27
Evaluable for Efficacy, n	23†
Median Age, years (range)	63 (43 - 83)
Male/Female	18 / 9
ECOG, 0/1/2	3 / 22 / 2
Median Creatinine Clearance, mL/min (range)	75 (45-135)
Prior Therapy Regimens, median (range)	1 (1 – 5)
Refractory to immediate prior therapy, n (%)	7 (26%)
Prior 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

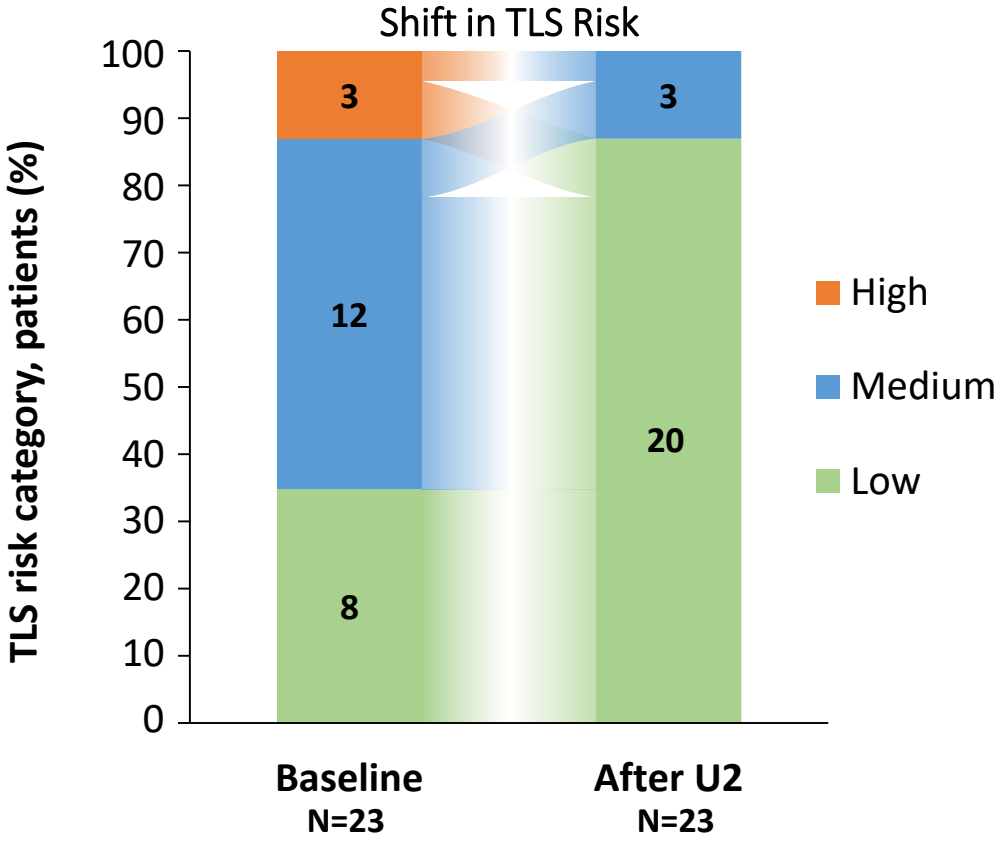
- DLT period: cycles 4 and 5
  - 1 DLT at 800 mg
    - Lower GI bleed, Cycle 5 (not related)
    - Resolved in 3 days
- MTD not reached

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

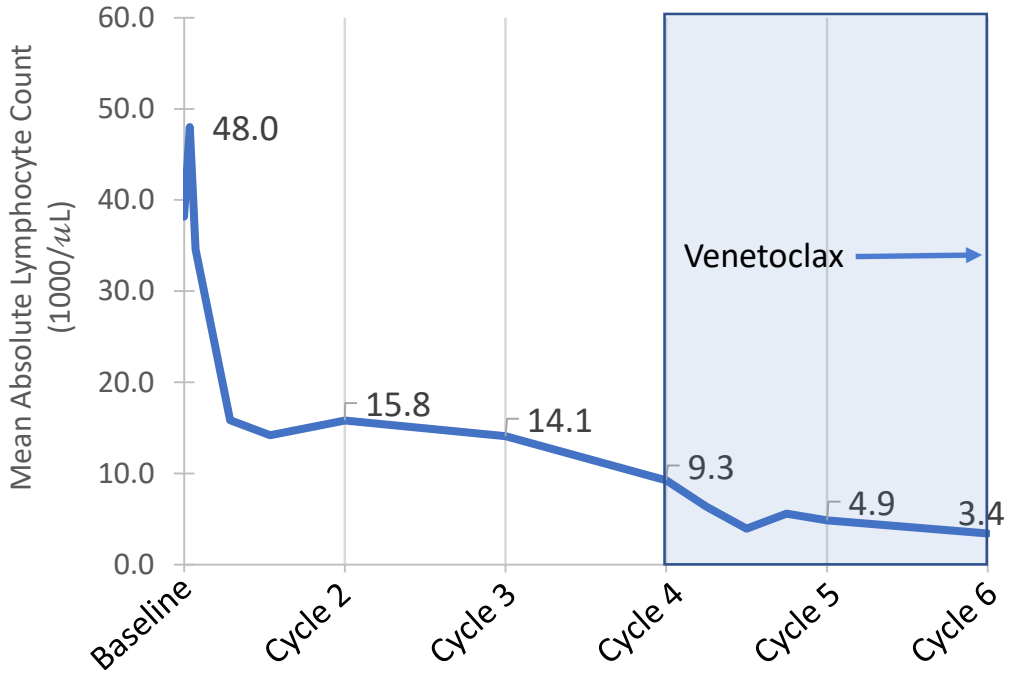
3 Cycles of U2 Induction Reduces Venetoclax TLS risk



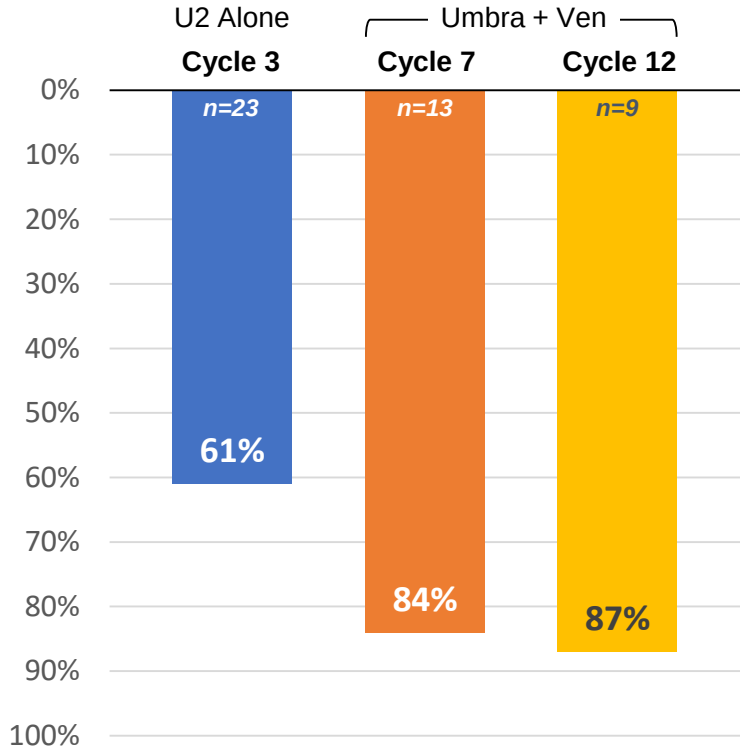
- After 3 cycles of ublituximab and umbralisib debulking:
  - No TLS High-Risk patients remaining
  - No patients developed clinical or laboratory TLS during venetoclax ramp up

Efficacy

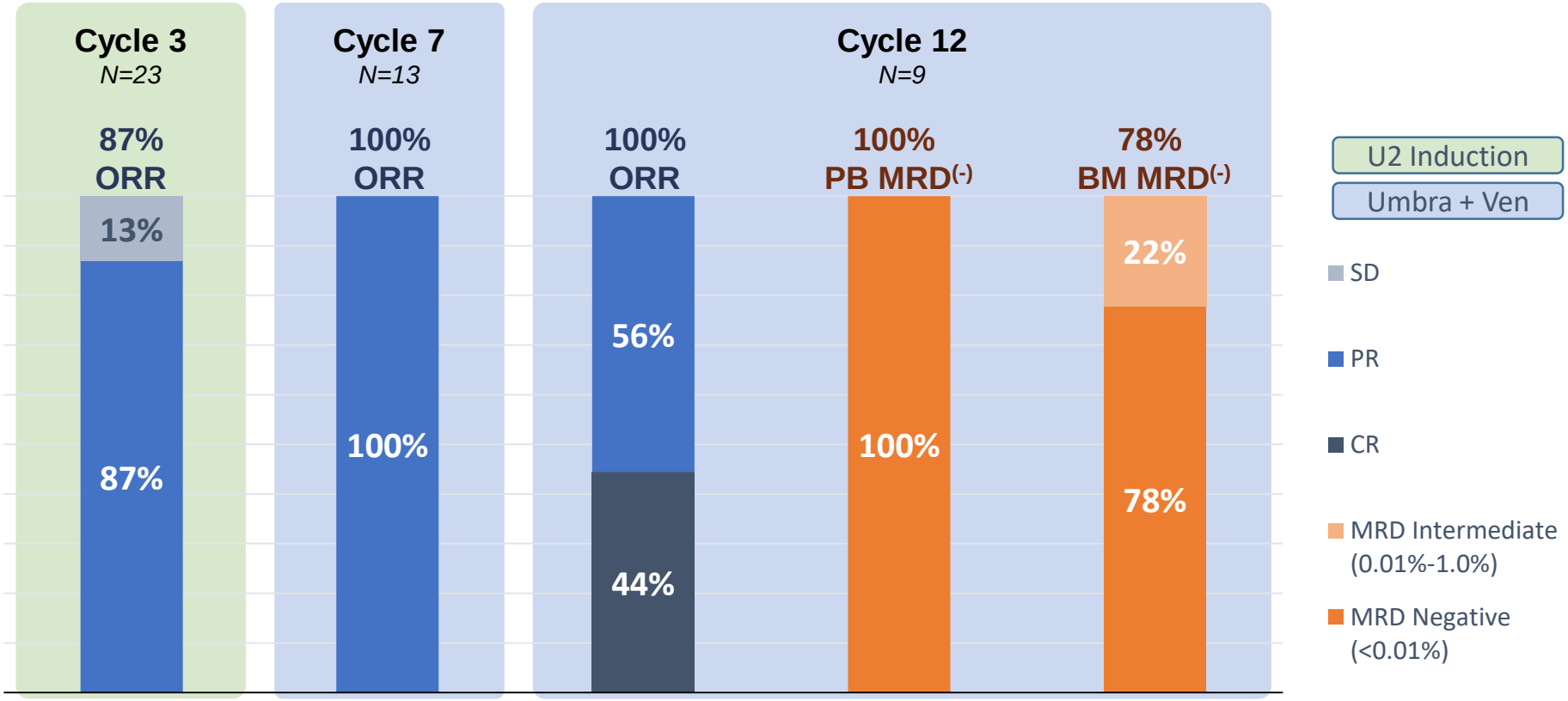
ALC Reduction Through Cycle 6



Mean % Lymph Node Reduction from Baseline

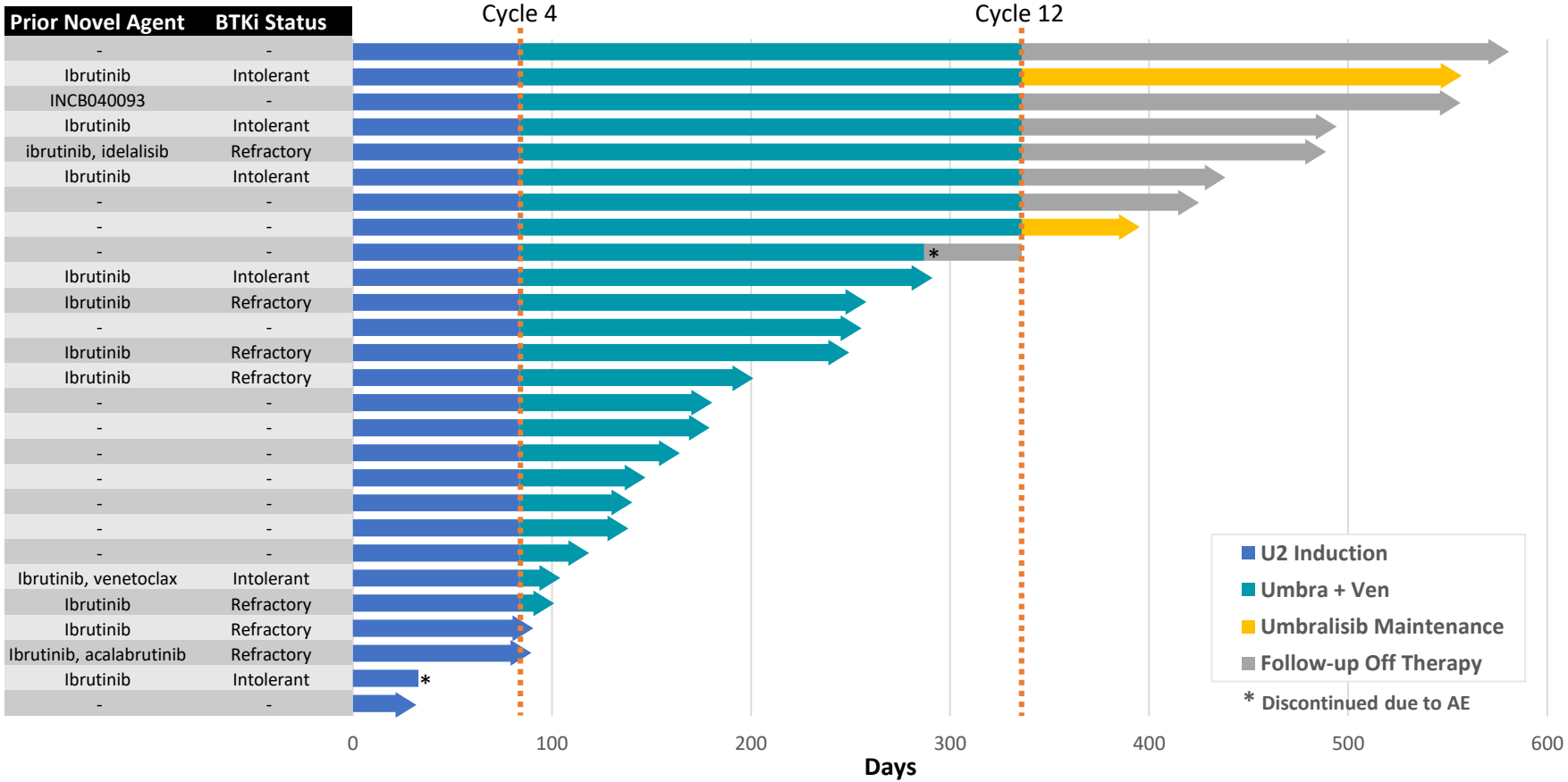


Efficacy: Response and MRD

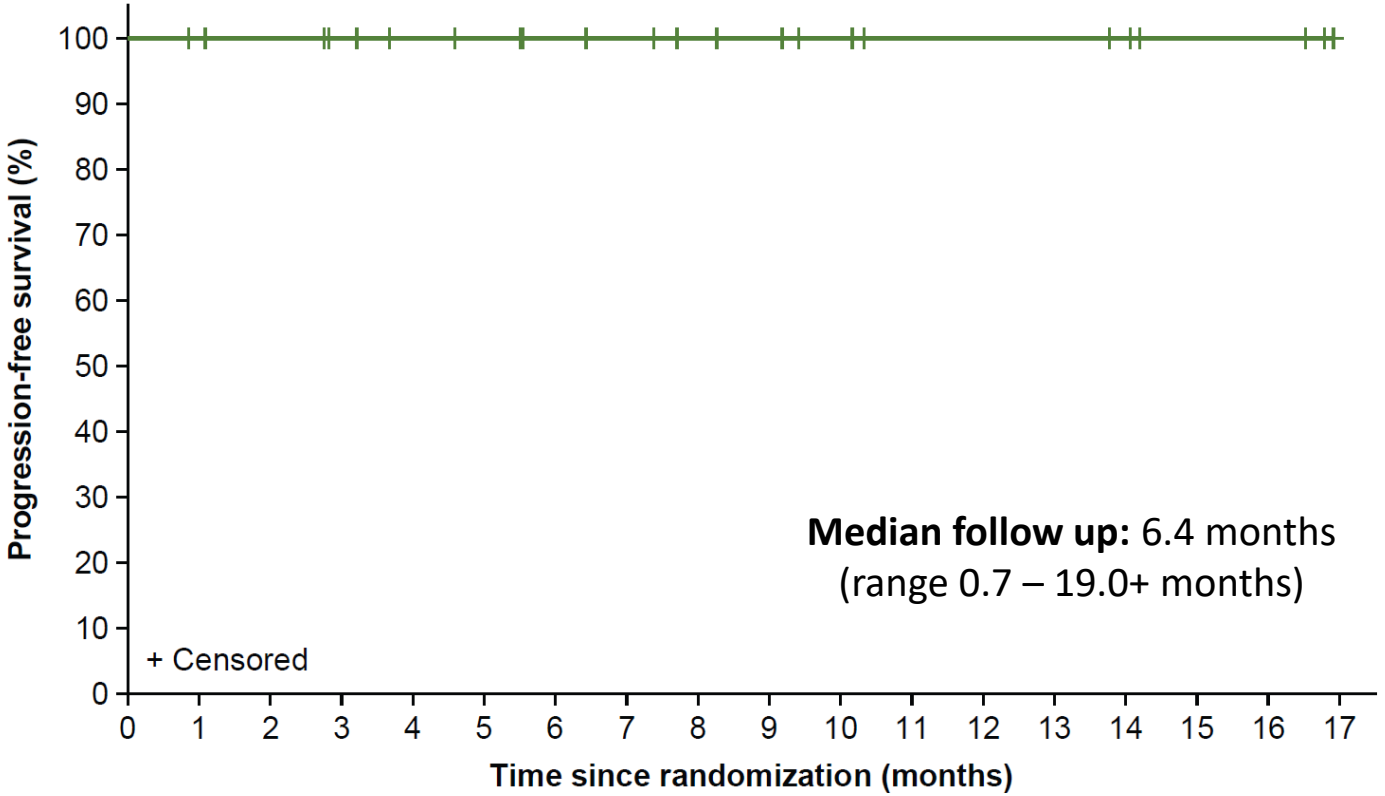


Cycle 3 & 7 Assessments were by CT only without BM, therefore CR could not be assessed

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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