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

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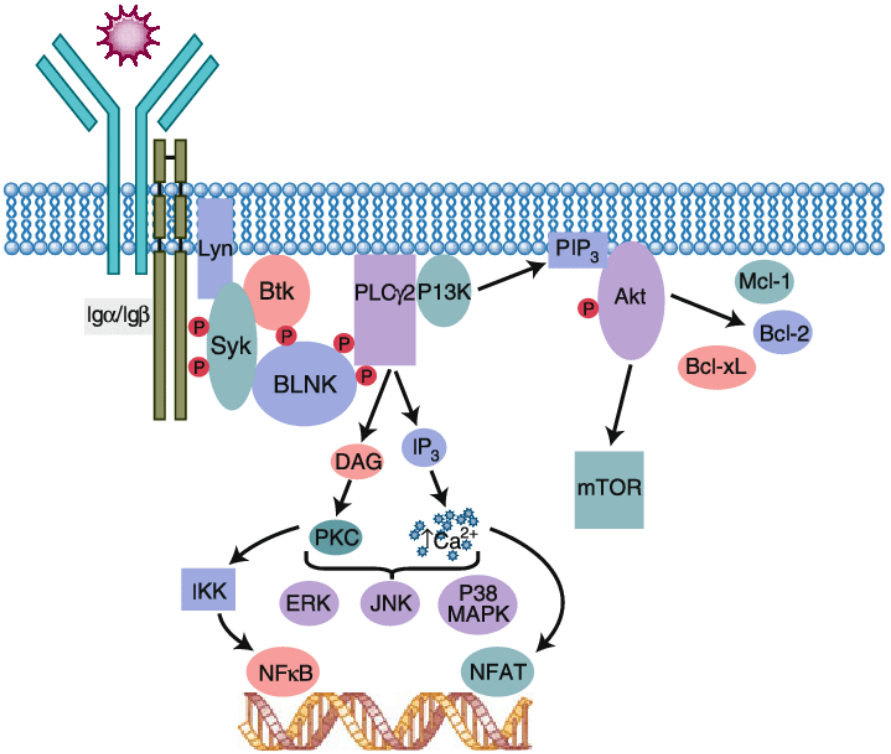
Background / Rationale: Venetoclax

- Inhibition of BCR signaling and BCL2 has been shown to be 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
  - Achieve undetectable MRD in relapsed refractory CLL patients



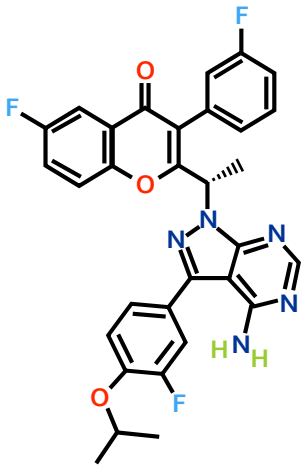
Cervantes-Gomez F et al. *Cancer Res.* 2015;21:3705-3715
Choudhary et al. *Cell Death Dis* 2015 Jan 15;6:e1593

Figure adapted from Riches et al., 2011

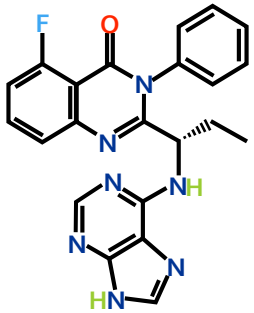
Background / Rationale: Umbralisib + Ublituximab (U2)

- Umbralisib is a 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 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

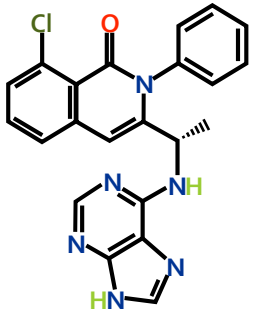
Umbralisib[1]



Idelalisib[1]



Duvelisib[1]



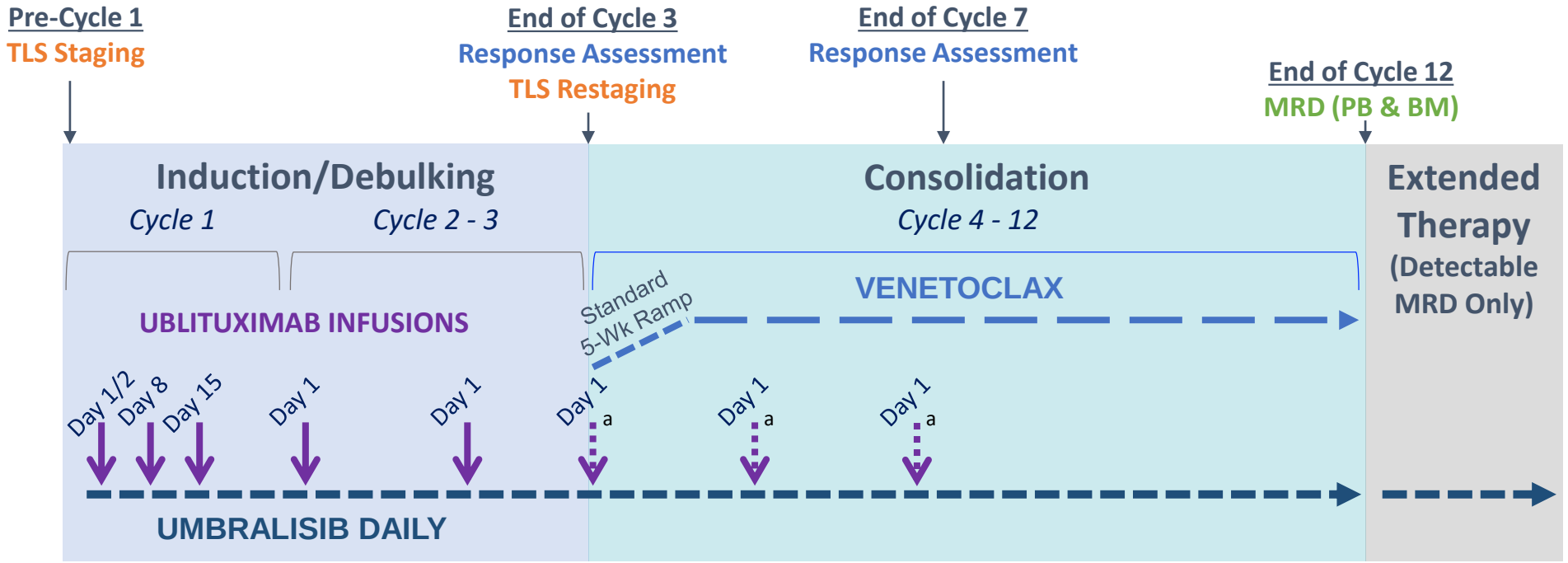
Isoform	K_d (nM)		
PI3kα	>10000	600	40
PI3Kβ	>10000	19	0.89
PI3Kγ	1400	9.1	0.21
PI3Kδ	6.2	1.2	0.047
CK1ε	180	>30,000	>30,000

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

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)
  - Undetectable MRD rate after 12 cycles of therapy
    - Centrally conducted 8-color flow cytometry

Study Design and Treatment



- [a]Protocol amended June 11th 2019 to add ublituximab infusions (900mg) on Day 1 of Cycles 4, 5, and 6 *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	43
Evaluable for Efficacy, n	39[†]
Median Age, years (range)	64 (43 - 83)
Male/Female	31 / 12
ECOG, 0/1/2	5 / 36 / 2
Prior Therapy Regimens, median (range)	2 (1 – 6)
Refractory to immediate prior therapy, n (%)	14 (33%)
Prior anti-CD20, n (%)	32 (74%)
Prior chemoimmunotherapy, n (%)	30 (70%)
Prior BTKi (ibrutinib / acalabrutinib), n (%)	25 (58%)
Refractory to prior BTK	13/25 (52%)
BTK or PLCγ mutation detected	7/8 (88%)*
Prior PI3Ki, n (%)	2 (5%)
Prior venetoclax, n (%)	1 (2%)

Molecular Aberrations

High Risk Features:	**n/N (%)**
11q deletion	13/43 (30%)
17p deletion	11/43 (26%)
TP53 mutation	7/40 (18%)
NOTCH1 mutation	7/26 (27%)
SF3B1 mutation	4/26 (15%)
IGHV unmutated	25/34 (74%)
At least 1 high risk feature	**34/43 (79%)**

[†]2 patients too early to evaluate, 2 not evaluable – came off prior to first response assessment

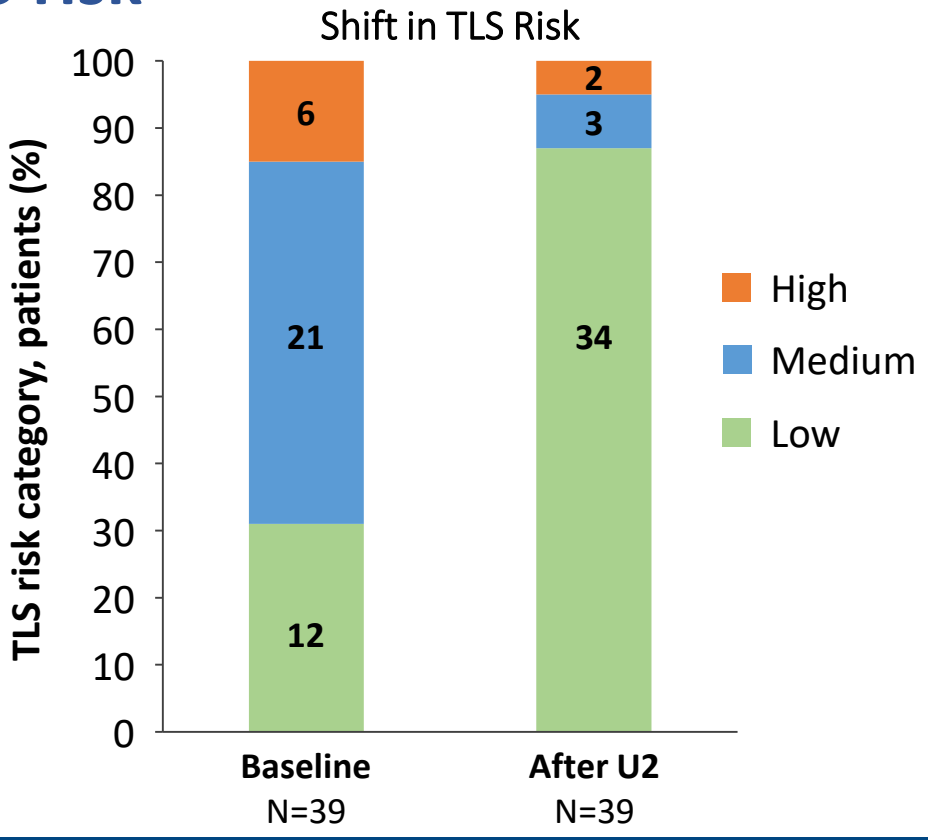
*8 patients were tested

All Causality AEs >20% (N=43)

	All Grades		Grade 3/4	
	N	%	N	%
Infusion reaction	26	60%	3	7%
Anemia	24	56%	2	5%
Thrombocytopenia	23	53%	-	-
Neutropenia	22	51%	9	21%
Creatinine increase	21	49%	-	-
Leukopenia	20	47%	5	12%
Fatigue	18	42%	-	-
Diarrhea	17	40%	2	5%
Nausea	15	35%	-	-
AST increase	13	30%	-	-
Alkaline phos increase	11	26%	-	-
Cough	11	26%	-	-
ALT increase	9	21%	-	-

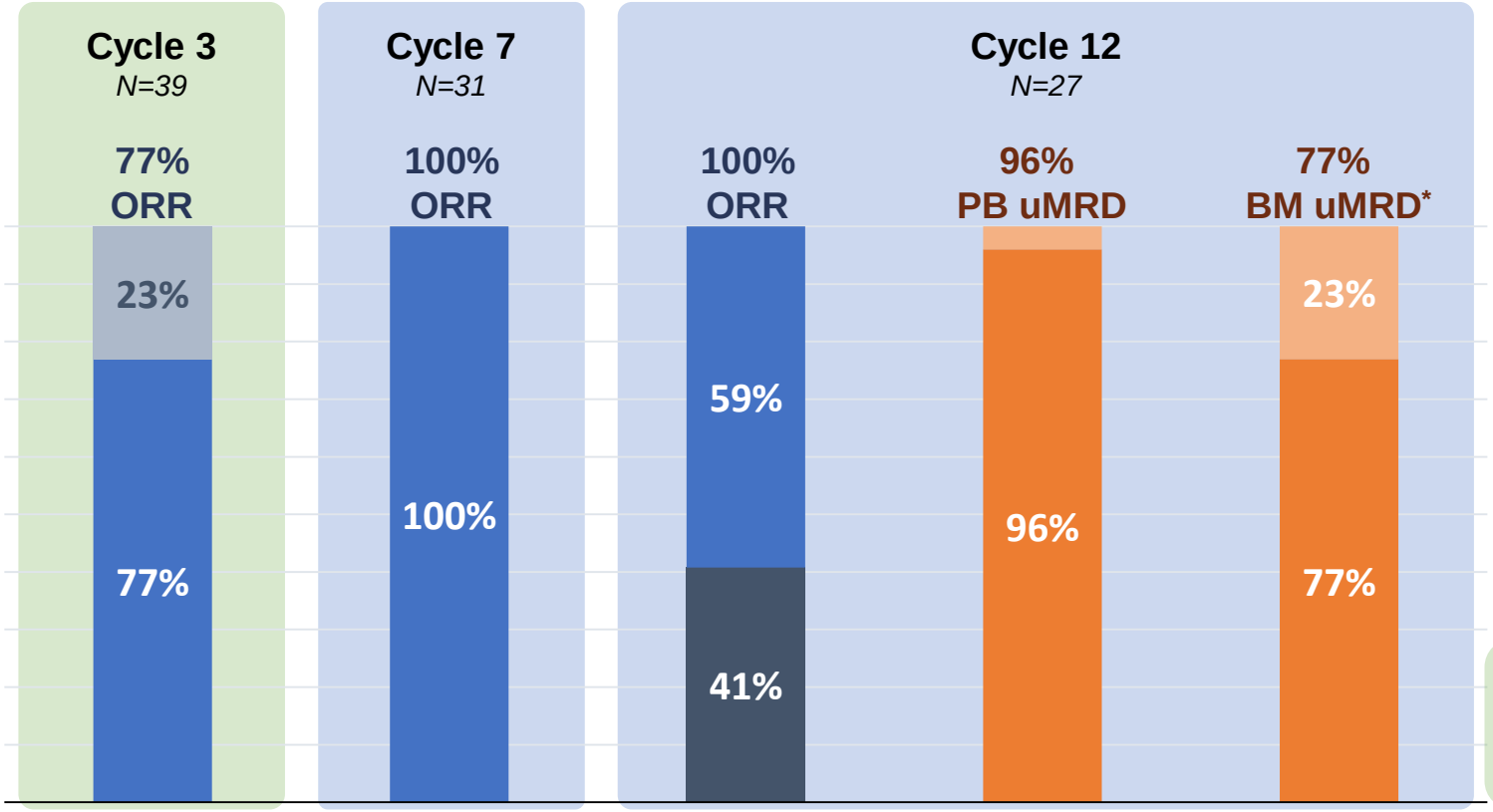
- G3/4 AEs of Special Interest:
  - Lung Infection/Pneumonia: 3 (7%)
  - Colitis: 2 (5%)
  - TLS: 1 (2%) - ublituximab related, prior to ven infusion
  - Rash: 1 (2%)
  - Pneumonitis: 0
  - No grade 3/4 LFT elevations
- Umbralisib dose reduced in 2 (4%) patients
- Umbralisib discontinued in 4 (9%) patients
- Venetoclax discontinued in 2 (4%) patients

3 Cycles of U2 Induction Reduces Venetoclax TLS risk



- After 3 cycles of ublituximab and umbralisib debulking:
  - 81% 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

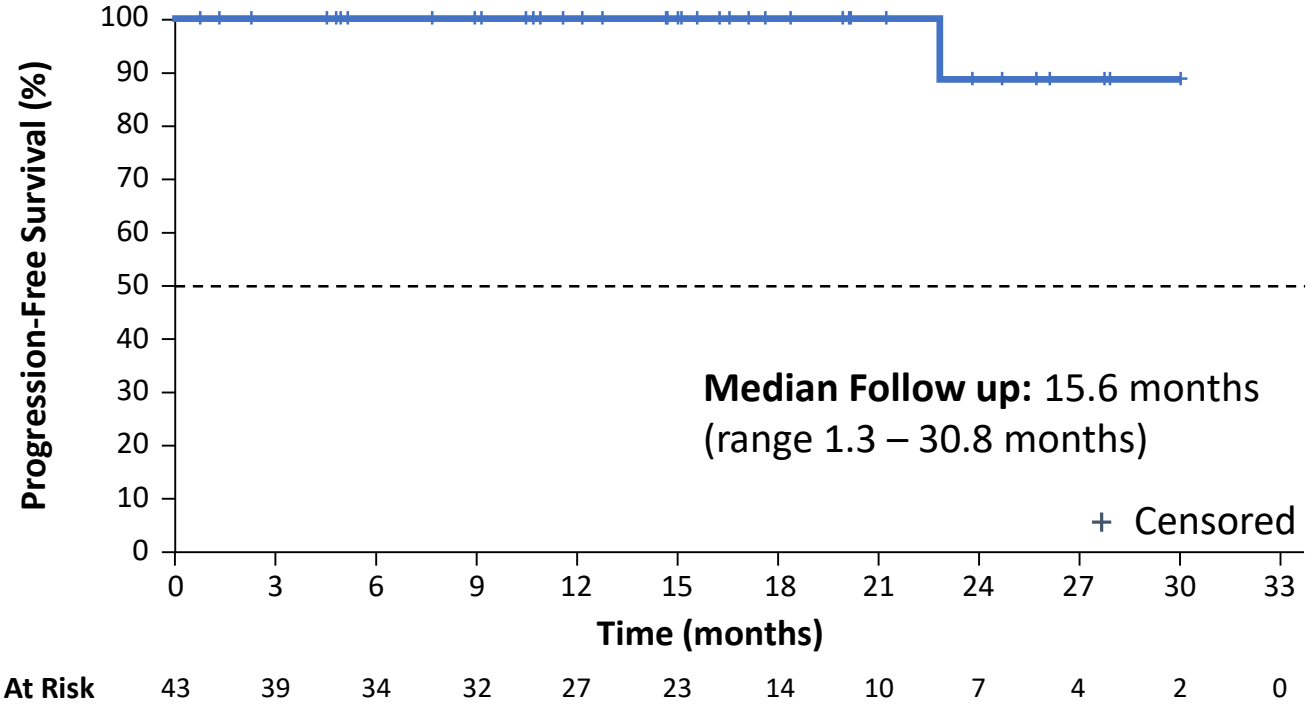


At Cycle 3, **64%** ORR in BTK-refractory patients, 74% for all patients with prior BTKi

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

*1 BM sample was not analyzed, *N=26*

Progression-free survival (n=43)



- **1 patient progressed 10 months after achieving uMRD in PB and BM and stopping therapy**

Conclusions

- Umbralisib, ublituximab and venetoclax is well tolerated at the Phase 2 doses
  - U2 induction mitigates TLS risk
  - Only 3 out of 43 (7%) patients discontinued the U2-Ven regimen prior to cycle 12
- Encouraging efficacy in relapsed/refractory CLL patients including those refractory to prior BTKi
  - 100% ORR, 41% CR rate at cycle 12
  - Undetectable MRD of 96% (26/27) and 77% (20/26) in peripheral blood and bone marrow, respectively
  - Only 1 patient has progressed and re-treatment strategies are being investigated
- Expansion cohorts for Richter's transformation and mantle cell lymphoma
- ULTRA-V: Phase 2 Study of U2-Ven in treatment naïve and relapsed/refractory CLL is ongoing

Acknowledgments

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- Participating Centers:

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