

# A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib (U2) to Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL): a Minimal Residual Disease (MRD)-driven, Time-limited Approach

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# | Disclosures

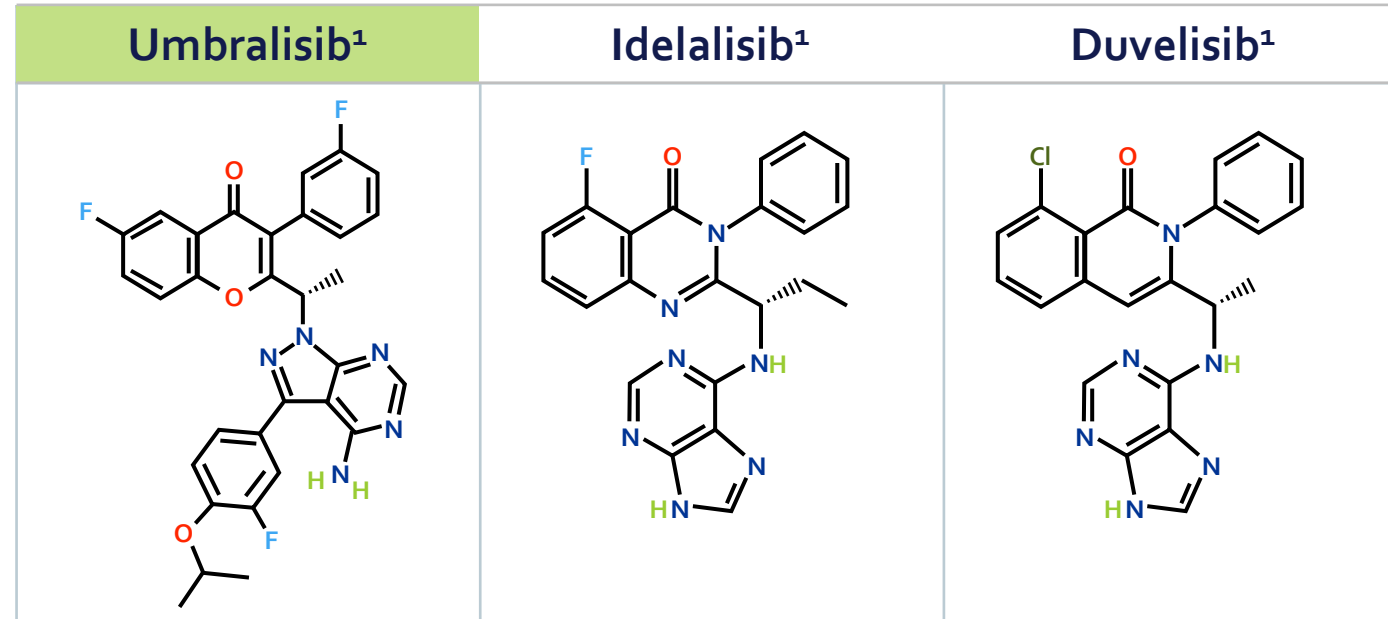
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# What is the Optimal Novel Agent Combination Therapy Approach for Patients with CLL?

- Time-limited combination therapies have demonstrated high ORR and durable responses for patients with CLL, but also have high rates of AEs and may overtreat favorable-risk patients.
- Patients receiving continuous ibrutinib monotherapy are at risk of cumulative toxicity and acquired resistance.
- After a period of ibrutinib monotherapy, could we identify a subset of patients with a response but persistent MRD who would most benefit from a combination novel agent approach? Could we convert their planned continuous therapy to a time-limited approach?
- This study utilized an “add-on” approach after a period of ibrutinib monotherapy exposure
  - Selecting patients who have detectable MRD may prevent overtreatment of those who can achieve deep remission with fewer agents
  - Patients are treated until achieving uMRD, consistent with discontinuing treatment based on depth of response
  - Durability of remission following treatment discontinuation is monitored with sequential MRD assessments

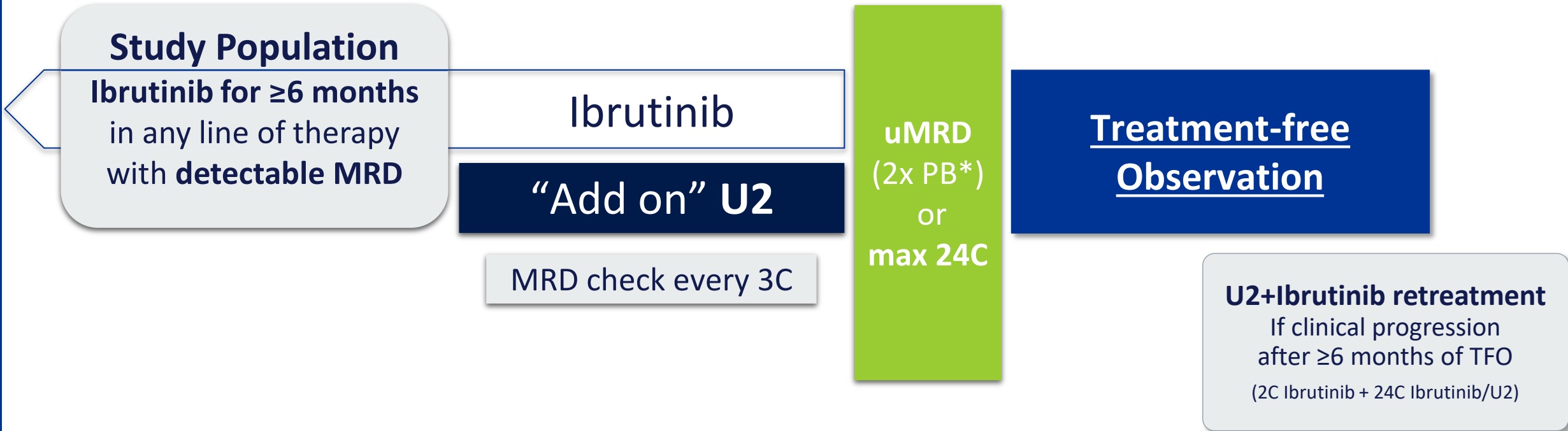
# Umbralisib and Ublituximab (U2) Added to Ibrutinib

- Umbralisib is an oral, once daily, selective inhibitor of phosphoinositide 3-kinase delta (PI3K $\delta$ ) and casein kinase-1epsilon (CK1 $\epsilon$ )
  - Preclinical: Greater retention of T-reg suppressive capacity compared to idelalisib & duvelisib<sup>2</sup>
  - Clinical: Integrated analysis of long-term safety demonstrates low rates of immune-mediated toxicity<sup>3</sup>
- Ublituximab is a novel 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



Isoform	Umbralisib <sup>1</sup>	Idelalisib <sup>1</sup>	Duvelisib <sup>1</sup>
PI3K $\alpha$	>10000	600	40
PI3K $\beta$	>10000	19	0.89
PI3K $\gamma$	1400	9.1	0.21
PI3K $\delta$	6.2	1.2	0.047
CK1 $\epsilon$	180	>30,000	>30,000

# Study Design



\* Flow cytometry, threshold  $10^{-4}$

## Treatment Regimen

- Umbralisib 800mg PO QD
- Ublituximab 900 mg IV C1 D1/2, 8, 15 C2-6 D1, and D1 every 3C
- Ibrutinib (previously tolerated dose)

## Primary Endpoint:

- Rate of uMRD
- Sample size based on uMRD target ≥25%*

## Key Secondary Endpoints:

- Safety, time to uMRD, PFS, TTP, OS, response to retreatment

# Baseline Characteristics

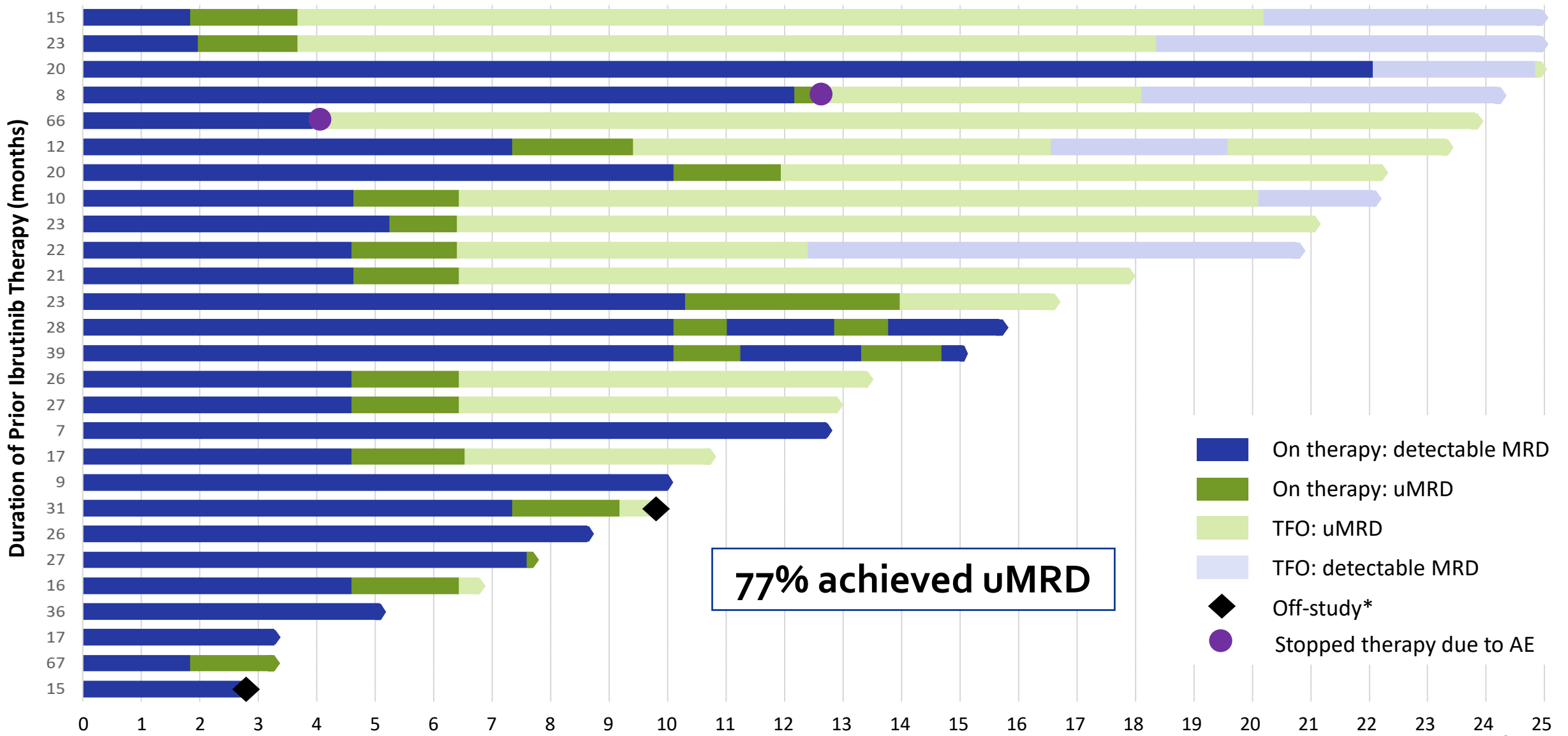
Evaluable for safety, n	28
Evaluable for efficacy, n	27 <sup>a</sup>
Median age, years (range)	64 (48 - 81)
Male, n (%)	22 (79%)
ECOG, 0/1/2, n	26/2/0
Median duration on ibrutinib prior to U2, mos (range)	21 (7 - 67)
Best response to ibrutinib (CR/PR/SD)	0/28/0
Ibrutinib as first-line treatment, n (%)	19 (68%)
Ibrutinib as treatment for relapsed/refractory disease	9 (32%)
Prior therapy regimens (excluding current ibrutinib), median (range)	1 (1-2)
Prior chemotherapy, n (%)	9 (100%)
<b>Molecular and cytogenetic Features, n/N (%)</b>	
IGHV unmutated	18/27 (67%)
11q deletion	6/28 (21%)
17p deletion	2/28 (7%)

# Treatment-emergent Adverse Events, All Causality (>10%)

Adverse Event, n (%) N=28	All Grades	Grades 3/4
Diarrhea	9 (32%)	1 (4%)
Hypertension	5 (18%)	2 (7%)
Anemia	5 (18%)	.
Contusion	5 (18%)	.
Fatigue	5 (18%)	.
ALT/AST increased	4 (14%)	1 (4%)
Cough	4 (14%)	.
Headache	4 (14%)	.
Nausea	4 (14%)	.
COVID-19	3 (11%)	1 (4%)
Decreased appetite	3 (11%)	.
Weight decreased	3 (11%)	.

- Two patients discontinued all therapy due to AEs:
  - One patient discontinued due to rash
  - A second patient discontinued due to a rash and arthralgias
  - Both patients were uMRD at the time of treatment discontinuation
- One patient died due to COVID-19 complications – 103 days after discontinuing U2

# Duration on Therapy

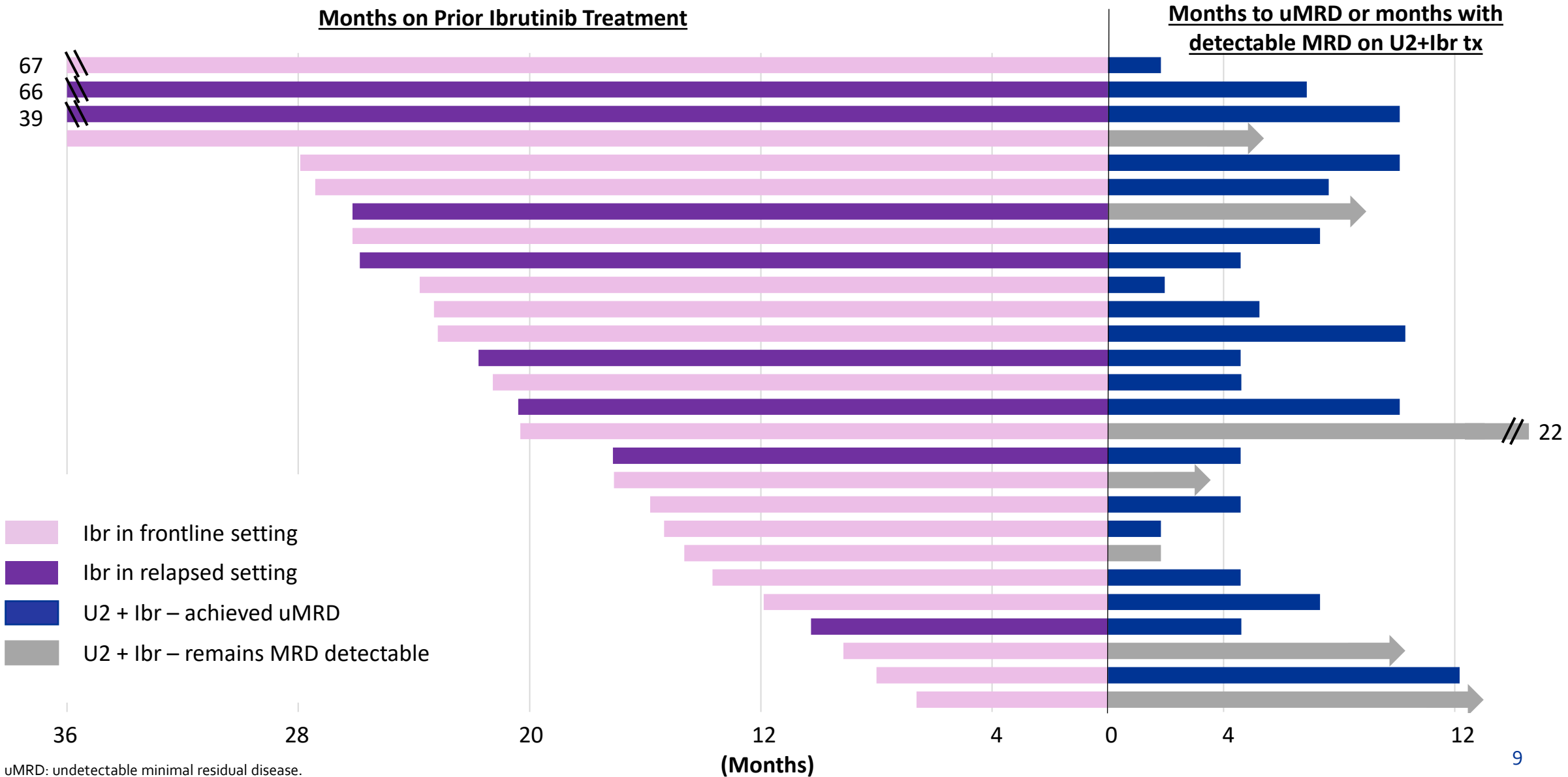


**77% achieved uMRD**

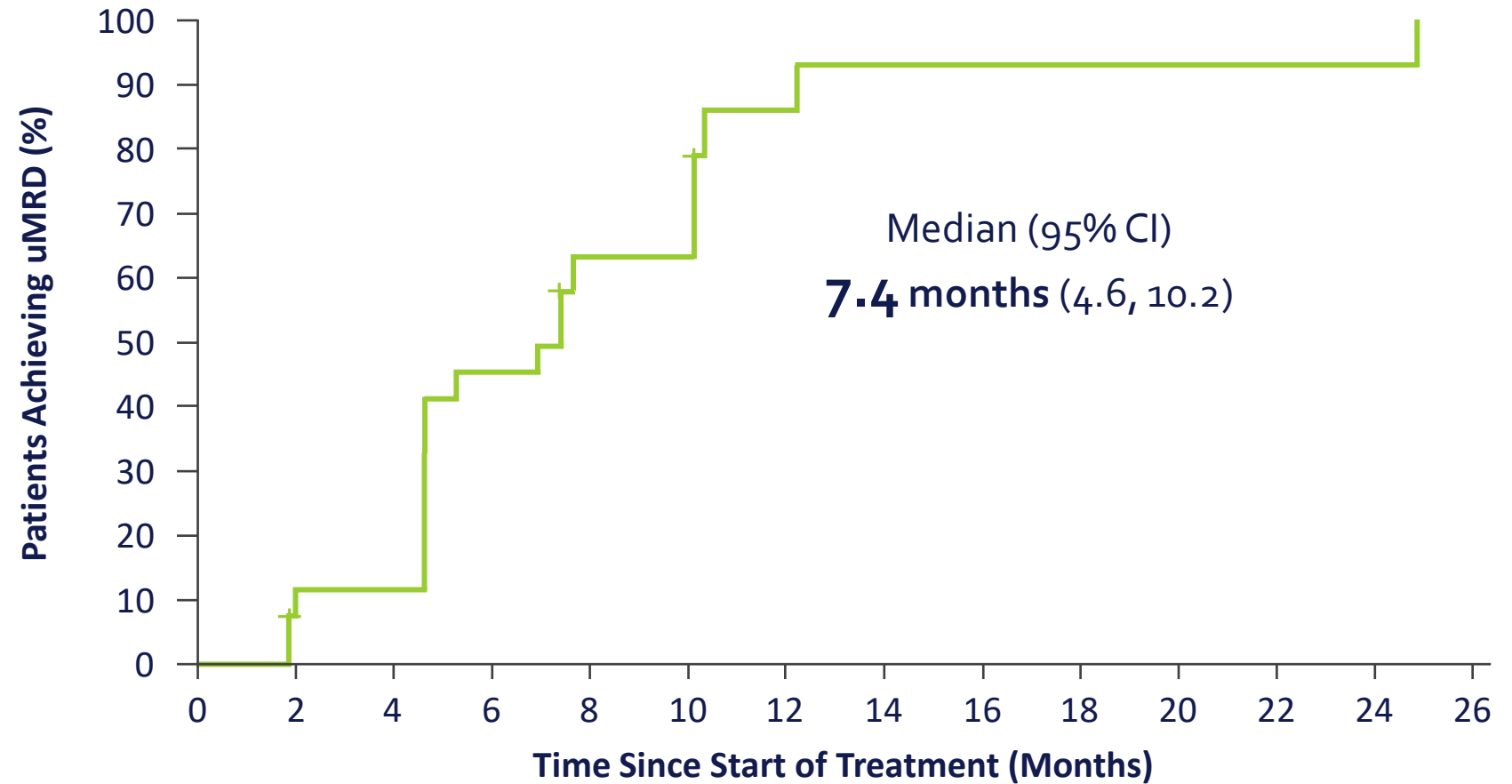
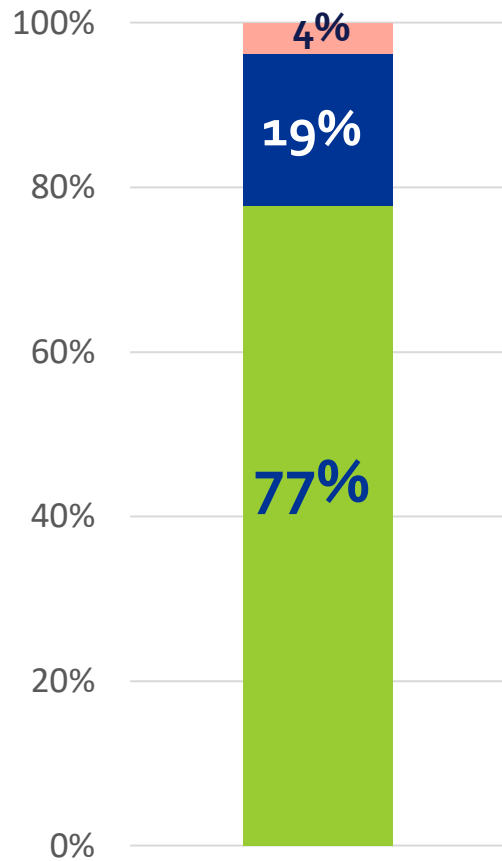
TFO: treatment-free observation; uMRD: undetectable minimal residual disease. \*1 patient withdrew consent from the study and 1 patient came off study due to disease progression



# Duration on Prior Ibrutinib and Time to First uMRD



# Proportion Achieving uMRD, Time to First uMRD



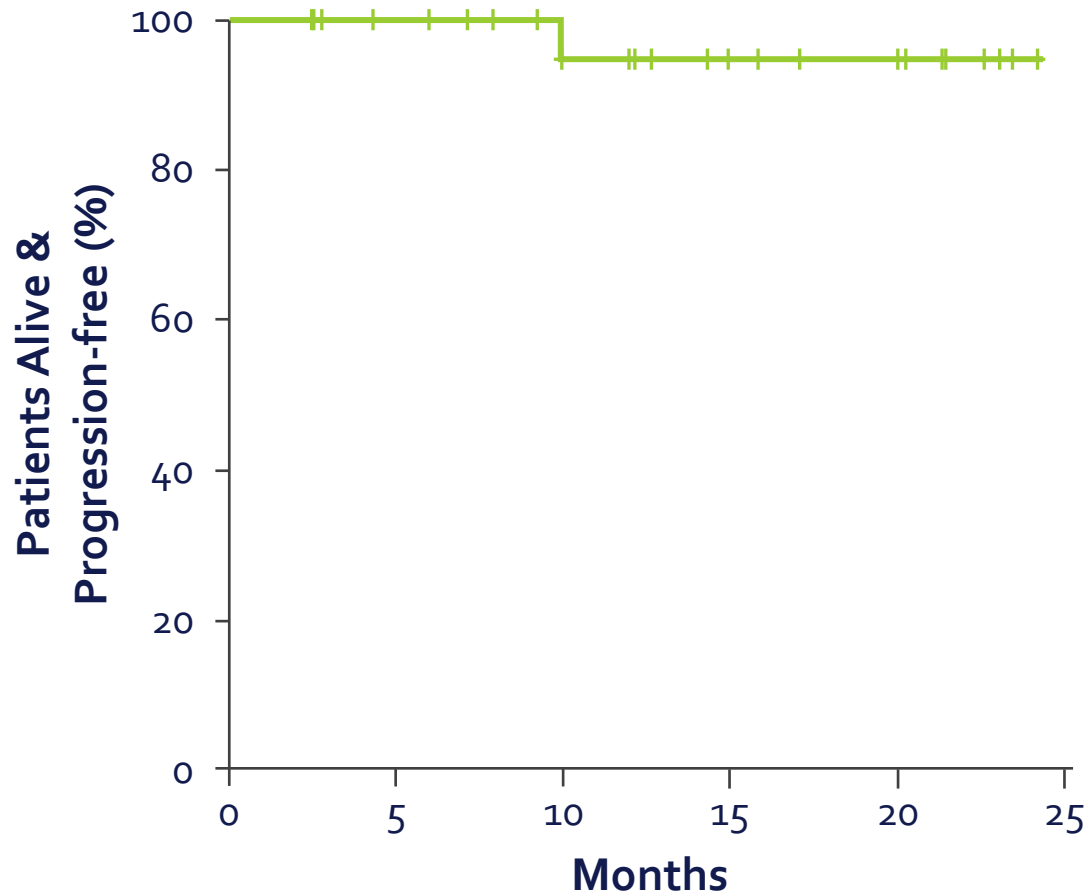
At Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26
	27	22	21	13	7	7	2	1	1	1	1	1	1	0

- Detectable MRD, off tx
- Detectable MRD, on tx
- At least one uMRD assessment\*

TX: treatment; uMRD: undetectable minimal residual disease. \*Includes any patient with at least one uMRD timepoint regardless of treatment status

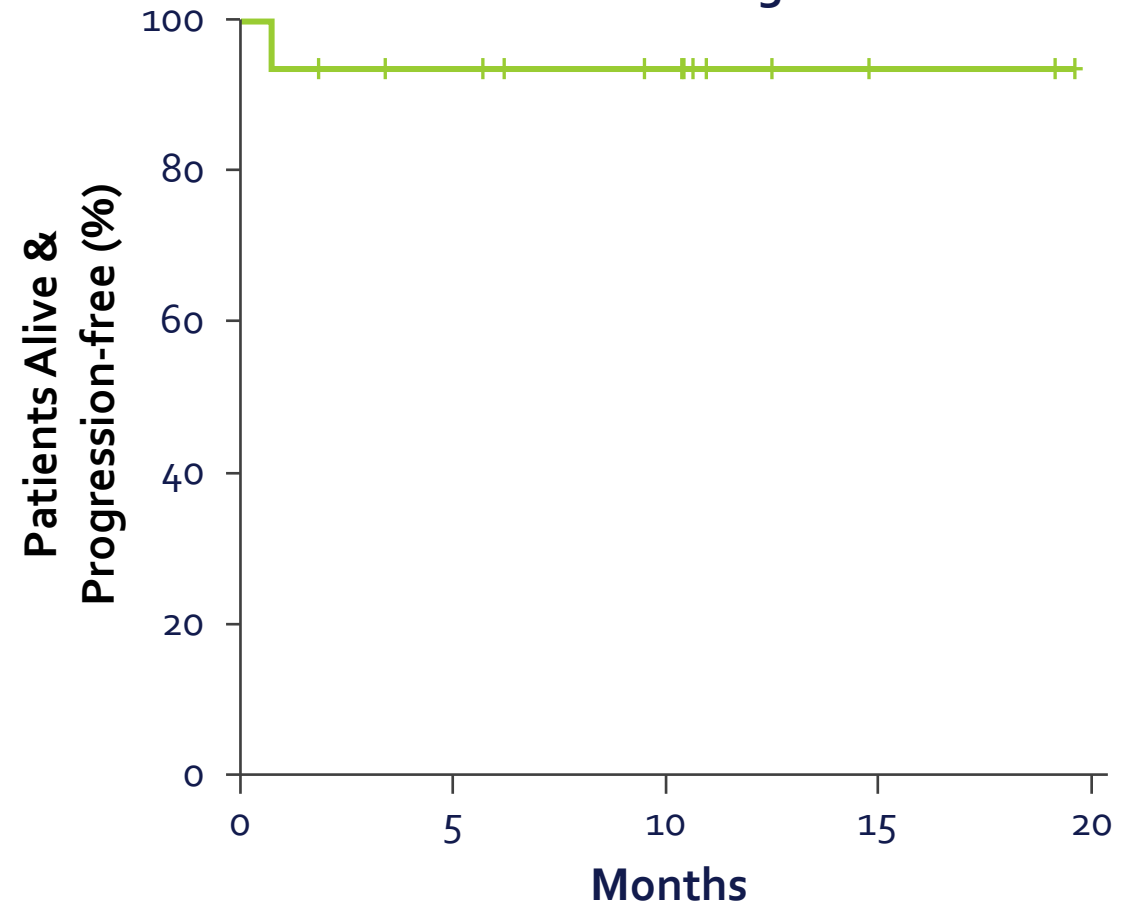
# Progression-free Survival

Progression-free Survival  
from Study Entry



At Risk 27 23 17 12 10 0

Progression-free Survival  
from Entering TFO



At Risk 15 12 9 3 0



# Conclusions

- This is the first non-venetoclax-containing MRD-driven, time-limited approach utilizing the combination of BTKi, PI3Ki, and anti-CD20 monoclonal antibody.
- The AE profile of ibrutinib remained unchanged with the addition of U2 therapy.
- This novel agent combination therapy was well tolerated and effective, with achievement of uMRD in 77% of evaluable patients.
- This “add-on” approach for patients on continuous ibrutinib resulted in deep remissions that allowed for a tailored, time-limited therapy and sustained treatment-free observation.
- Study continues to enroll with other cohorts exploring the addition of U2 to acalabrutinib or venetoclax.

# Acknowledgements

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