Clinical activity of TG-1701, as monotherapy and in combination with Ublituximab and Umbralisib (U2), in patients with B-cell malignancies

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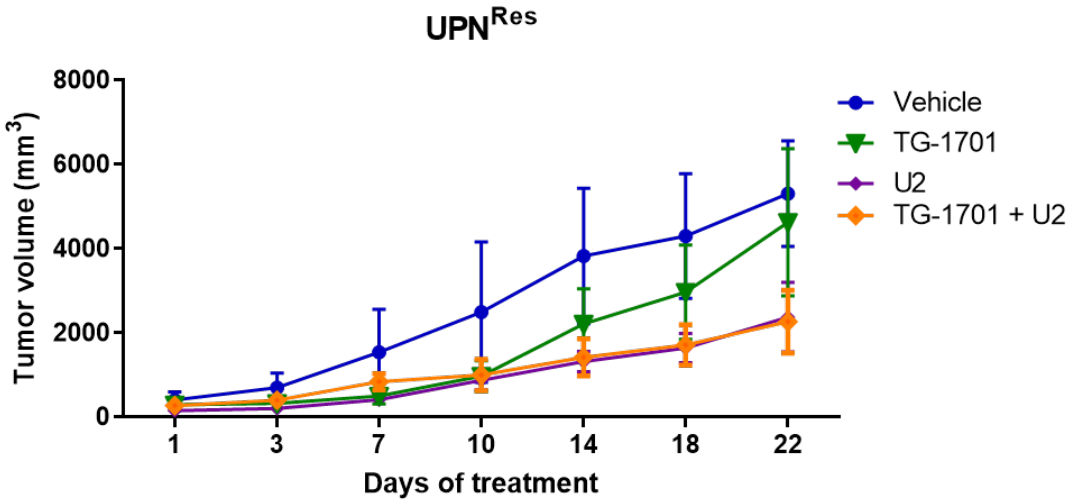
Background

- BTK inhibitors have changed the landscape of treatment in CLL, however deep remissions with BTK monotherapy are rare and many patients discontinue currently available BTK inhibitors due to intolerance
- TG-1701 is a once-daily (QD), covalently bound BTK inhibitor that exhibits superior selectivity compared with ibrutinib in an *in vitro* whole kinome screening[1]
- The triple combination of TG-1701 with umbralisib, a dual PI3Kδ/CK-1ε inhibitor, and ublituximab, a glycoengineered anti-CD20 antibody, inhibited tumor growth in BTK-resistant xenograft models[2]

Kinase Selectivity Profiling at 1uM[1]

Drug	Kinase inhibition IC50 (nM)						
	BTK	TEC	TXK	HER2	EGFR	ITK	JAK3
Acalabrutinib	5.1	93	368	1000	> 1000	> 1000	> 1000
TG-1701	3	4	136	> 3000	270	> 3000	> 3000
Ibrutinib	1.5	7	2	6.4	5.3	4.9	32

TG-1701+U2 inhibits growth in BTK resistant cell lines[2]



[1]Normant E, et al., EHA 2018 (absPF638); [2]Ribeiro M, et al. AACR 2020 (abs 2205); BTK: Bruton's tyrosine kinase, CK-1:casein kinase-1; PI3K: phosphatidylinositol 3-kinase

Methods

OBJECTIVES

- Characterize the safety profile of TG-1701
- Determine the RP2D of TG-1701 as monotherapy and in combination with U2
- PK, preliminary antitumor activity, BTK occupancy

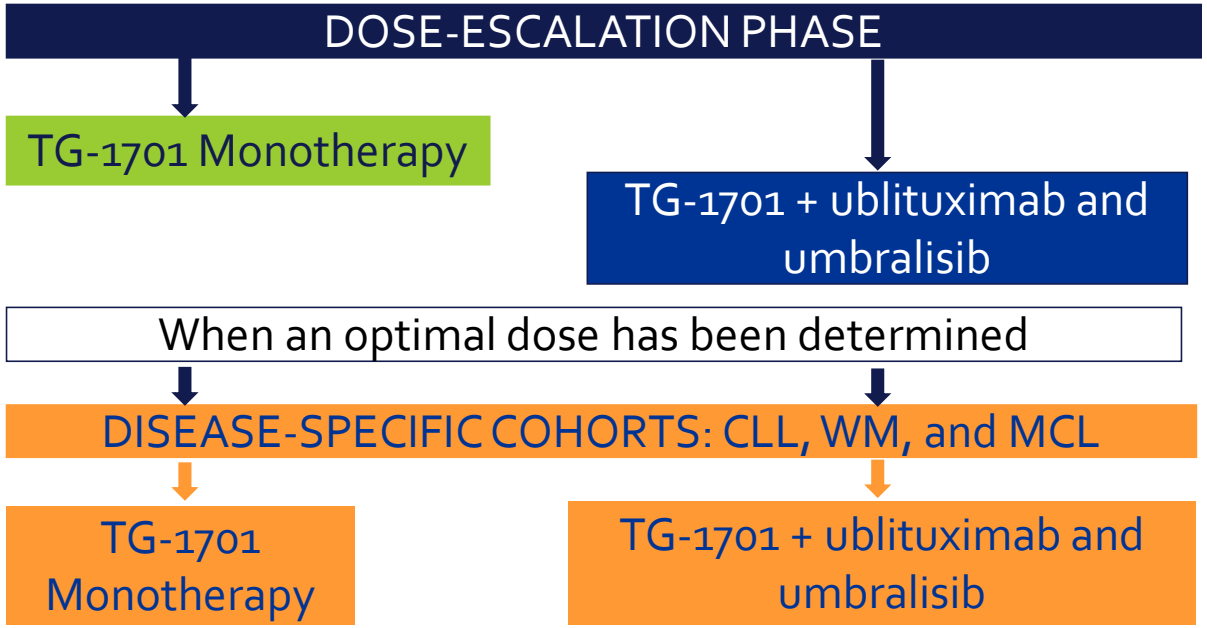
KEY INCLUSION CRITERIA

- R/R disease to prior standard therapy, histologically confirmed B-cell lymphoma or CLL, that warrants systemic therapy
  - For the Disease-specific Cohorts, previously untreated pts could be enrolled if unsuitable for standard front-line chemoimmunotherapy
- Adequate organ system function

KEY EXCLUSION CRITERIA

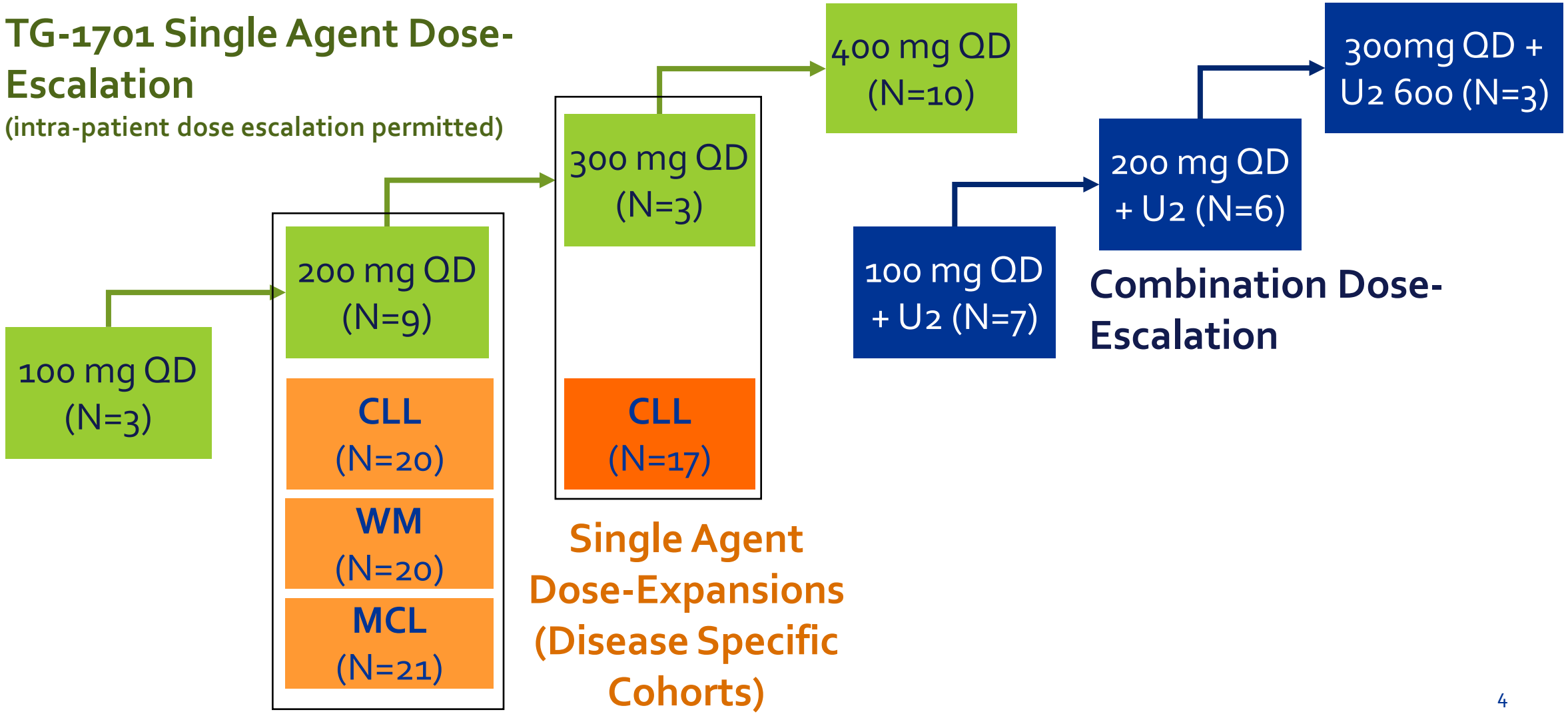
- Prior therapy with a BTK inhibitor; any severe or uncontrolled illness or condition; concomitant warfarin therapy (other anticoagulation is allowed)

STUDY SCHEMA



- Oral TG-1701 QD, continuously administered in 28-day (D) cycles (C). Intra-patient dose escalations are permitted in monotherapy arm.
- 1701 + U2 arm: escalating TG-1701 QD + umbralisib 800 mg oral QD (or 600 mg QD) + ublituximab 900 mg IV on D1, 8, 15 of C1, and D1 of C2 through C6, and D1 every 3 C thereafter.

Trial Design



Patient Demographics and Disease Characteristics

Characteristic	Dose-escalation Phase		Disease-specific Cohorts (200 mg QD)		
	TG-1701 (N = 25)	TG-1701 + U2 (N = 16)	CLL (N = 20)	WM (N = 20)	MCL (N = 21)
Male sex, N(%)	14 (56)	5 (31)	7 (35)	12 (60)	13 (62)
Age, years, median (min/max)	68 (49 / 86)	69 (47 / 79)	71 (53 – 87)	73 (57 – 92)	70 (57 – 85)
≥75 years, N(%)	*7 (28)*	*4 (25)*	*4 (20)*	*8 (40)*	*5 (24)*
ECOG 0 / 1 / 2 (%)	56 / 44 / 0	87 / 13 / 0	35 / 65 / 0	45 / 50 / 5	48 / 48 / 4
Prior therapies, median (range)	1 (1 - 5)	2 (1 - 5)	1 (0 – 5)	1 (0 – 4)	3 (0 – 10)
Refractory to last prior therapy, N(%)	7 (28)	2 (13)	2 (10)	3 (15)	4 (19)
Previous anti-CD20 therapy, N(%)	25 (100)	16 (100)	14 (93)*	12 (100)*	18 (100)*
Treatment-naïve, N(%)	-	-	5 (25)	8 (40)	3 (14)

*Calculation excludes treatment-naïve patients

Patient Disposition

Cutoff: Oct 28, 2020	Dose-escalation Phase		Disease-specific Cohorts	
	TG-1701 (N=25)	TG-1701 + U2 (N=16)	200 mg (N=61)	300 mg (N=17)
Pts continuing treatment, N(%)	18 (72)	16 (100)	53 (87)	17 (100)
Intra-pt dose escalation, N(%)	7 (28)	-	-	-
Dose reduction (any agent), N(%)	4 (16)	5 (31)	2 (3)	This cohort recently started enrollment and it is too early to report safety and efficacy
Pts off study, N(%)	7 (28)	-	8 (13)	
Reason for treatment discontinuation, N(%)				
Progression by criteria	5 (20)	-	5 (8)	
Clinical progression	-	-	1 (2)	
Due to AE	-	-	-	
Pt/physician decision	2 (8)	-	2 (3)	

All Causality AEs (≥10%) TG-1701 Monotherapy

Adverse event, N (%)	Dose escalation (100 to 400 mg) N=25		Disease-specific cohorts (200 mg) N=61	
	Any Grade	Grade 3	Any Grade	Grade ≥3
Constipation	8 (32)	-	3 (5)	-
Respiratory tract infection	7 (28)	1 (4)	4 (7)	-
Bruising	7 (28)	-	5 (8)	-
Fatigue	5 (20)	-	1 (2)	-
Rash	4 (16)	1 (4)	3 (5)	-
Nausea	4 (16)	-	1 (2)	-
Dizziness	3 (12)	-	1 (2)	-
Headache	3 (12)	-	4 (7)	-
Diarrhea	3 (12)	-	7 (11)	-
Epistaxis	3 (12)	-	2 (3)	-
Hematologic and lab abnormalities	**Any Grade**	**Grade 3**	**Any Grade**	**Grade ≥3**
Neutropenia	6 (24)	2 (8)	5 (8)	3 (5)
ALT increased	6 (24)	3 (12)[a]	2 (3)	1 (2)
AST increased	5 (20)	1 (4)	1 (2)	-
Anemia	4 (16)	-	4 (7)	3 (5)

- **There have been no G4 AEs in the dose escalation of monotherapy**
- **At target Phase 2 dose of 200mg QD (n=61), AE's of special interest were rare with G3 hypertension 1.6%, atrial fibrillation 1.6%, and no instances of major bleeding**

[a]All at 400 mg QD. 2 cases were brief episodes in asymptomatic pts with normal liver function (total bilirubin within normal range). 1 case was in the context of significant progression of disease in the liver.

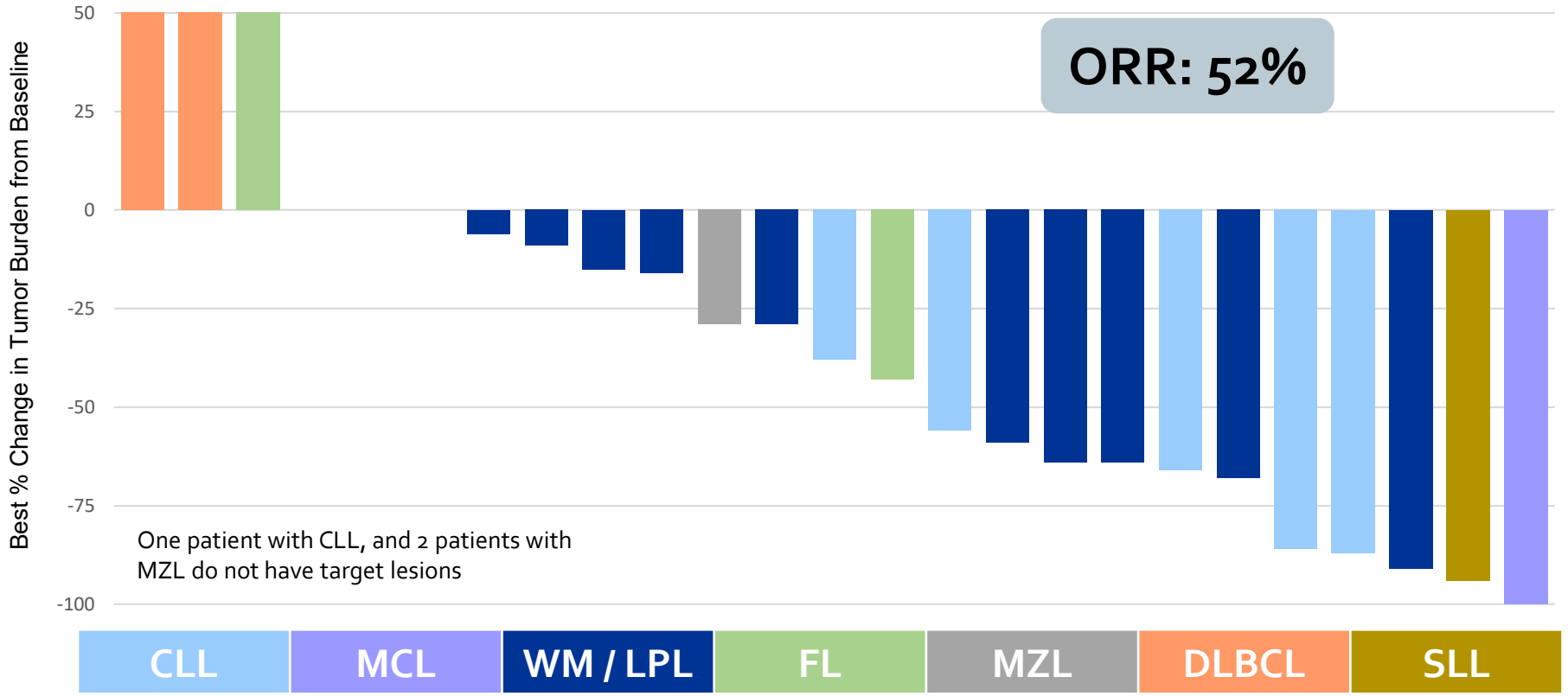
All Causality AEs (≥15%) TG-1701+U2 Combination Therapy

Adverse event, N(%)	Patients (N = 16)		
	Any Grade	Grade 3	Grade 4
Diarrhea	7 (44)	1 (6)	-
IRR[a]	6 (38)	-	-
Bruising	6 (38)	-	-
Nausea	5 (31)	1 (6)	-
Hypertension	4 (25)	1 (6)	-
Fatigue	4 (25)	-	-
Rash	3 (19)	-	-
Vomiting	3 (19)	-	-
Hematologic and laboratory abnormalities	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia	4 (25)	1 (6)	1 (6)
ALT increased	4 (25)	3 (19)[b]	1 (6)[c]
AST increased	4 (25)	3 (19)	-

[a]IRR: includes the terms "chest tightness", and "facial flushing".
[b]All cases of G3 ALT increased were in patients with normal liver function (total bilirubin within normal range). Two patients continue therapy at a reduced dose of umbralisib (600 mg and 400 mg). The third patient discontinued ublituximab due to serum sickness.
[c]The G4 ALT increased was symptomatic (vomiting) and with abnormal liver function, the patient has recovered with complete response and remains on study therapy.

Efficacy Dose Escalation (100-400mg) Monotherapy

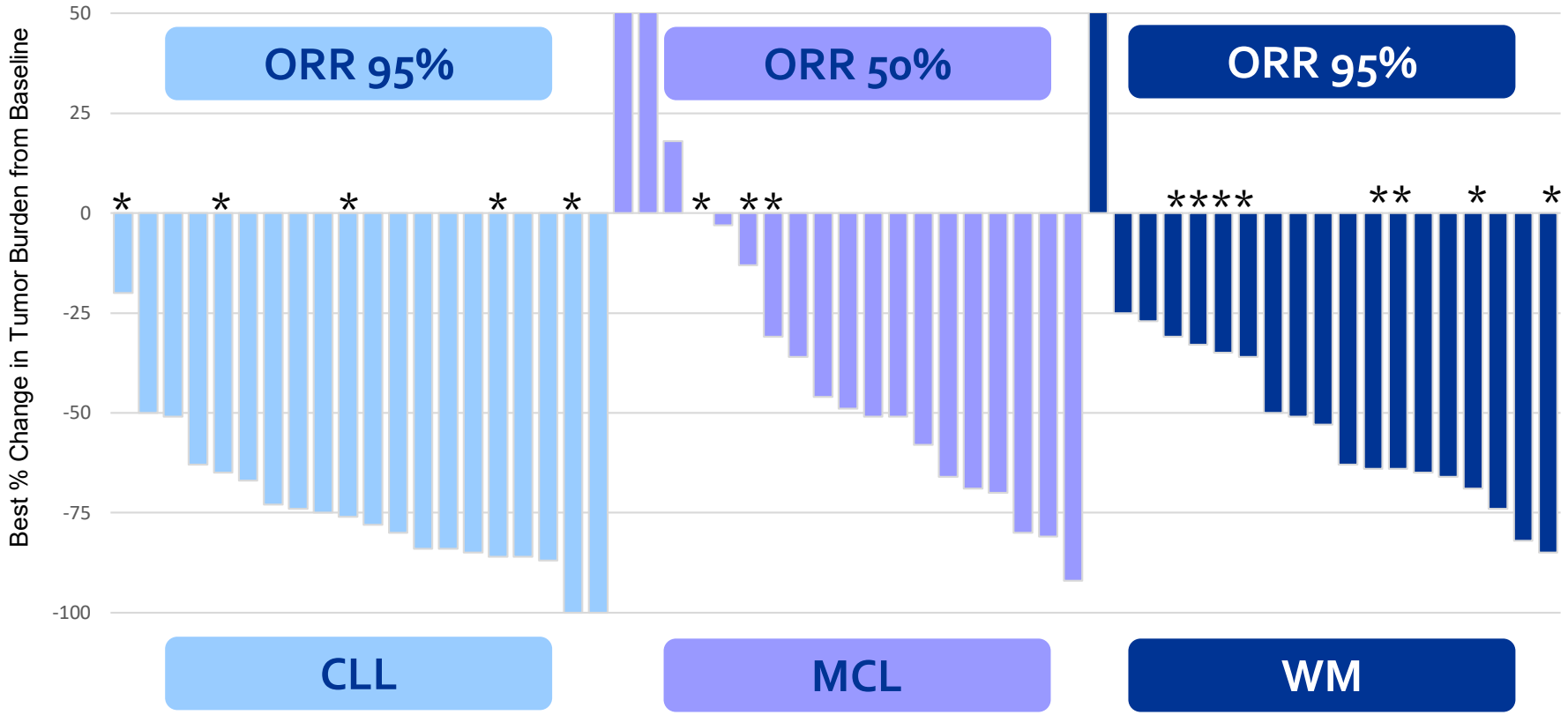
TG-1701 Dose-escalation
(100 to 400 mg QD)



- N = 23
- Median follow up: 14 mos (1-25)

Efficacy Disease Specific Cohorts Monotherapy (200mg)

TG-1701 Disease-specific Cohorts
(200 mg QD)

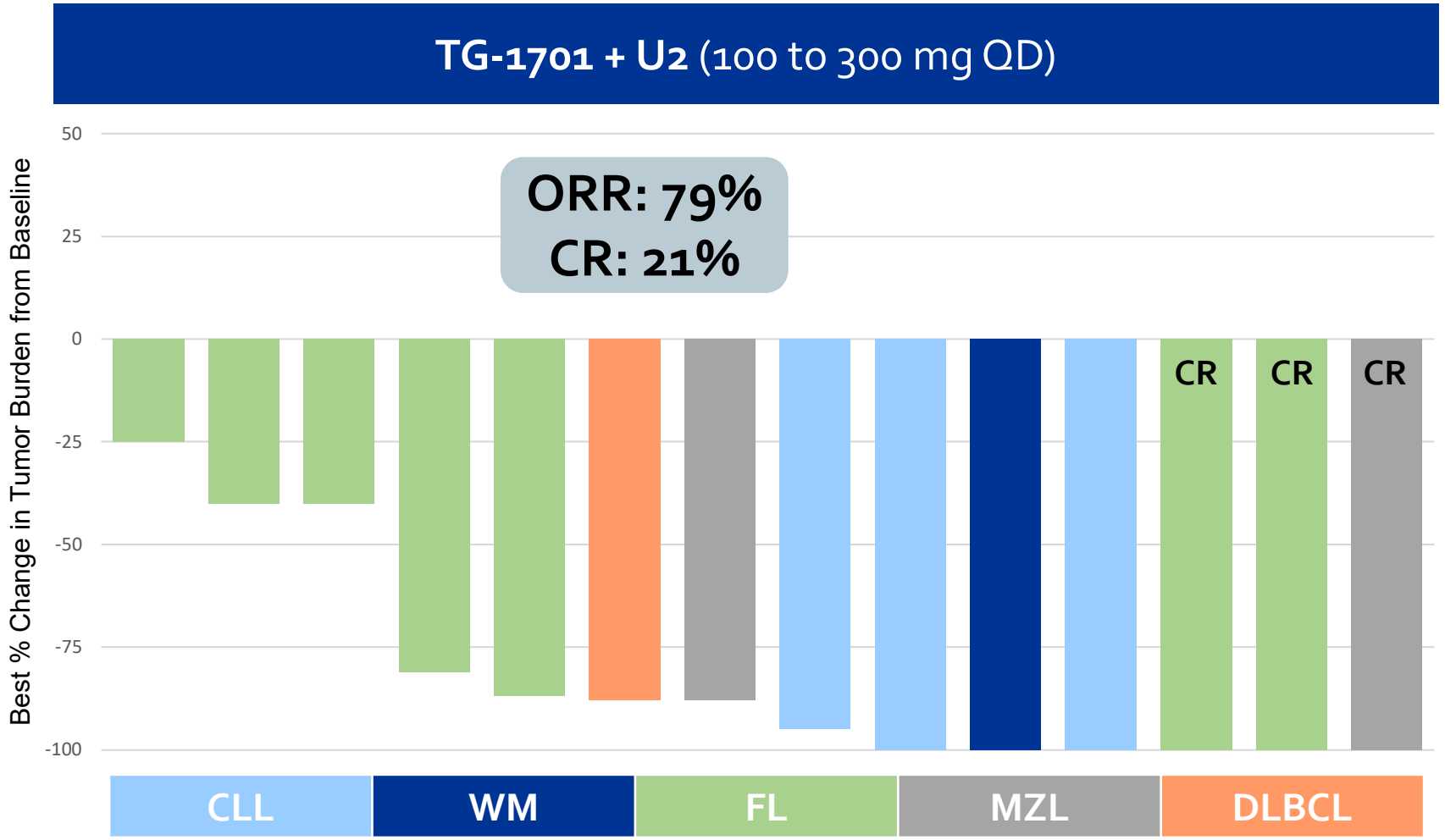


- N = 57
  - 20 CLL
  - 18 MCL
  - 19 WM
- Median follow up: 7 mos (1-12)

[a]One patient does not have measurable disease and is excluded from the denominator.

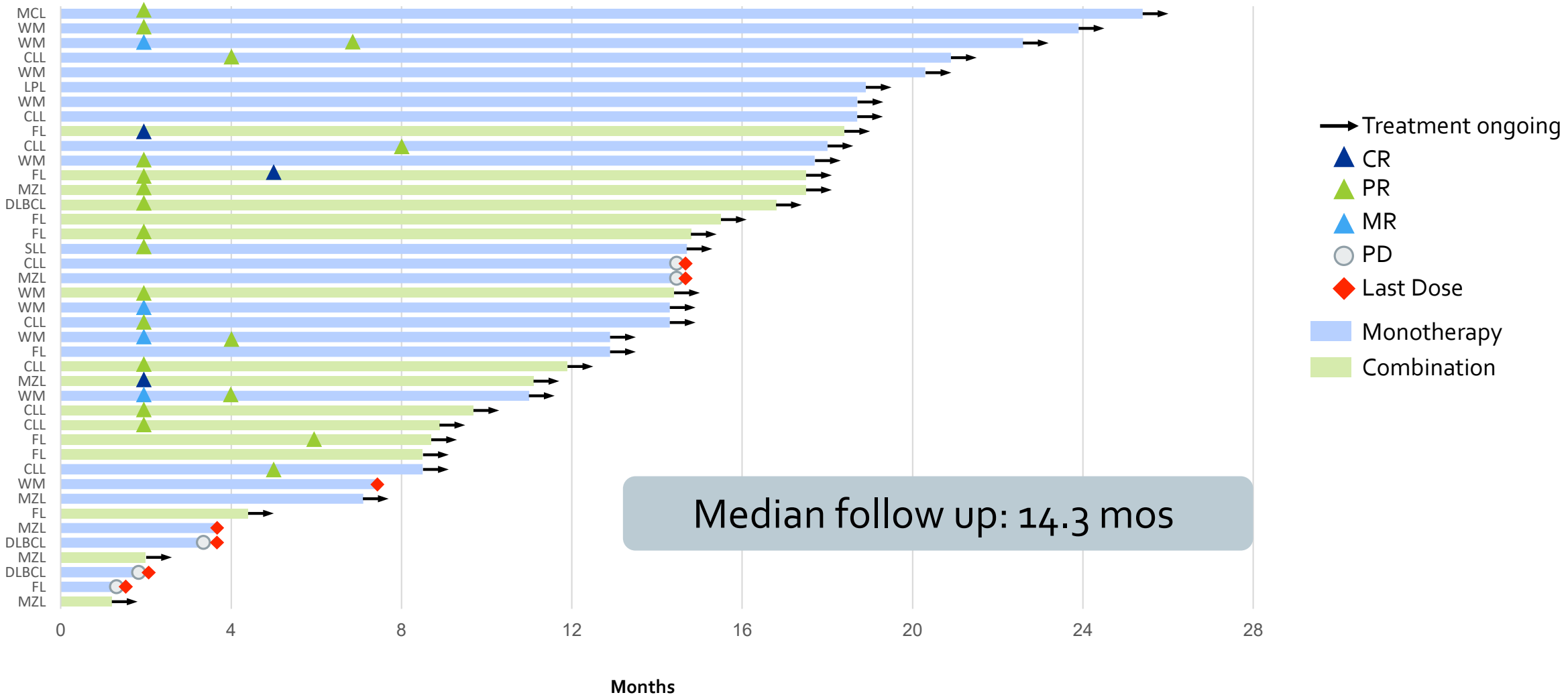
*Treatment naive

Efficacy TG-1701 + U2 Dose-escalation



- N = 14
- Median follow up: 12 mos (1-18)

Treatment Exposure and Response Duration
Dose Escalation Phase



Summary and Conclusions

- TG-1701 exhibits an encouraging safety profile, with clinical and pharmacodynamic activity at all dose levels evaluated that support QD dosing
- The MTD has not been achieved in the monotherapy arm (up to 400mg QD)
- The combination of TG-1701 with U2 has been well tolerated and dose escalation continues. Combination treatment is associated with encouraging clinical activity, including early complete responses
- This study (NCT03671590) continues enrollment and future registration trials are being planned

Acknowledgements

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