

# Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies

Chan Y. Cheah MBBS, DMSc<sup>1</sup>, Wojciech Jurczak MD<sup>2</sup>, Masa Lasica MBBS<sup>3</sup>, Nick Wickham MBBS<sup>4</sup>, Tomasz Wróbel MD<sup>5</sup>, Jan Walewski MD<sup>6</sup>, Costas K. Yannakou MBBS (Hons)<sup>7</sup>, Stanley Cheung MBBS<sup>4</sup>, Katharine L. Lewis MBBS<sup>1</sup>, Monika Długosz-Danecka MD, PhD<sup>2</sup>, Krzysztof Giannopoulos MD<sup>8</sup>, Hari P. Miskin MS<sup>9</sup>, Emmanuel Normant PhD<sup>9</sup>, Owen A. O'Connor, MD, PhD<sup>9</sup>, Alejandro D. Ricart MD<sup>9</sup>, Constantine S. Tam MBBS (Hons), MD<sup>3</sup>

<sup>1</sup>Linear Clinical Research, and Department of Haematology, Sir Charles Gairdner Hospital, Nedlands Western Australia, Medical School, University of Western Australia, Crawley, Western Australia; <sup>2</sup>Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; <sup>3</sup>St. Vincent Hospital and University of Melbourne, Melbourne, Victoria; <sup>4</sup>Ashford Cancer Centre Research, Adelaide, South Australia; <sup>5</sup>Wroclaw Medical University, Poland; <sup>6</sup>Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; <sup>7</sup>Department of Molecular Oncology and Cancer Immunology, Epworth HealthCare, East Melbourne, Victoria; <sup>8</sup>Hematology Department, St John's Cancer Centre, Lublin, Poland; <sup>9</sup>TG Therapeutics, Inc., New York, NY.

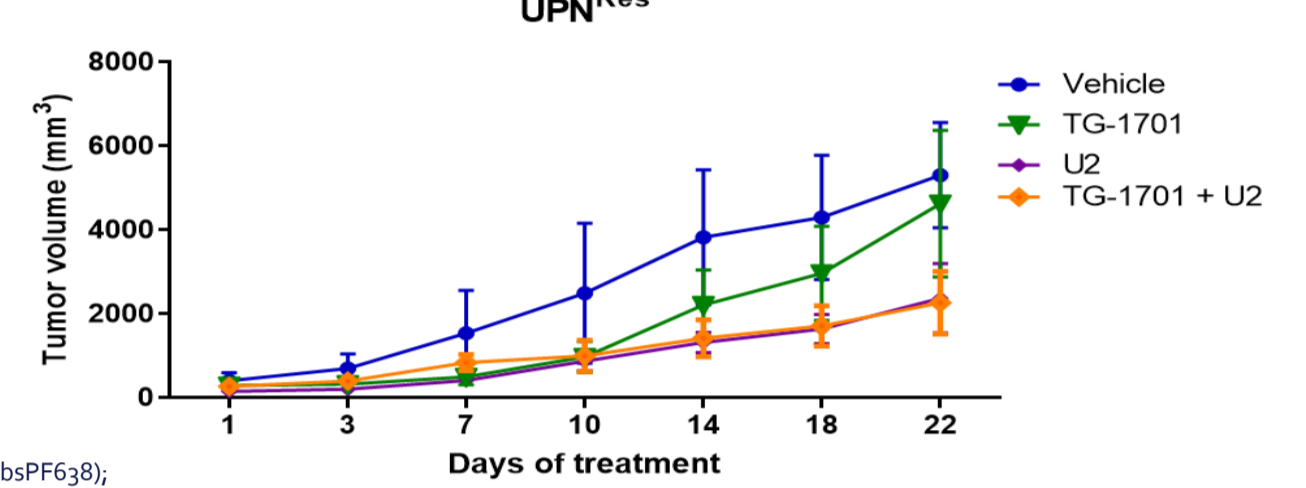
## BACKGROUND AND METHODS

- Deep remissions with BTK monotherapy in CLL are rare
- TG-1701 is a covalently bound BTK inhibitor with superior selectivity compared with ibrutinib<sup>1</sup>
- The triple combination of TG-1701 with umbralisib and ublituximab (U2) inhibited tumor growth in BTK-resistant xenograft models<sup>2</sup>

### Kinase Selectivity Profiling at 10μM in an *in vitro* whole kinome screening<sup>3</sup>

Drug	Kinase inhibition IC <sub>50</sub> (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<sup>2</sup>



<sup>1</sup>Normant E, et al., EHA 2018 (abstr 5038)  
<sup>2</sup>Ribeiro M, et al. AACR 2020 (abstr 2205). BTK: Bruton's tyrosine kinase; CK-1: casein kinase-1; PI3K: phosphatidylinositol 3-kinase

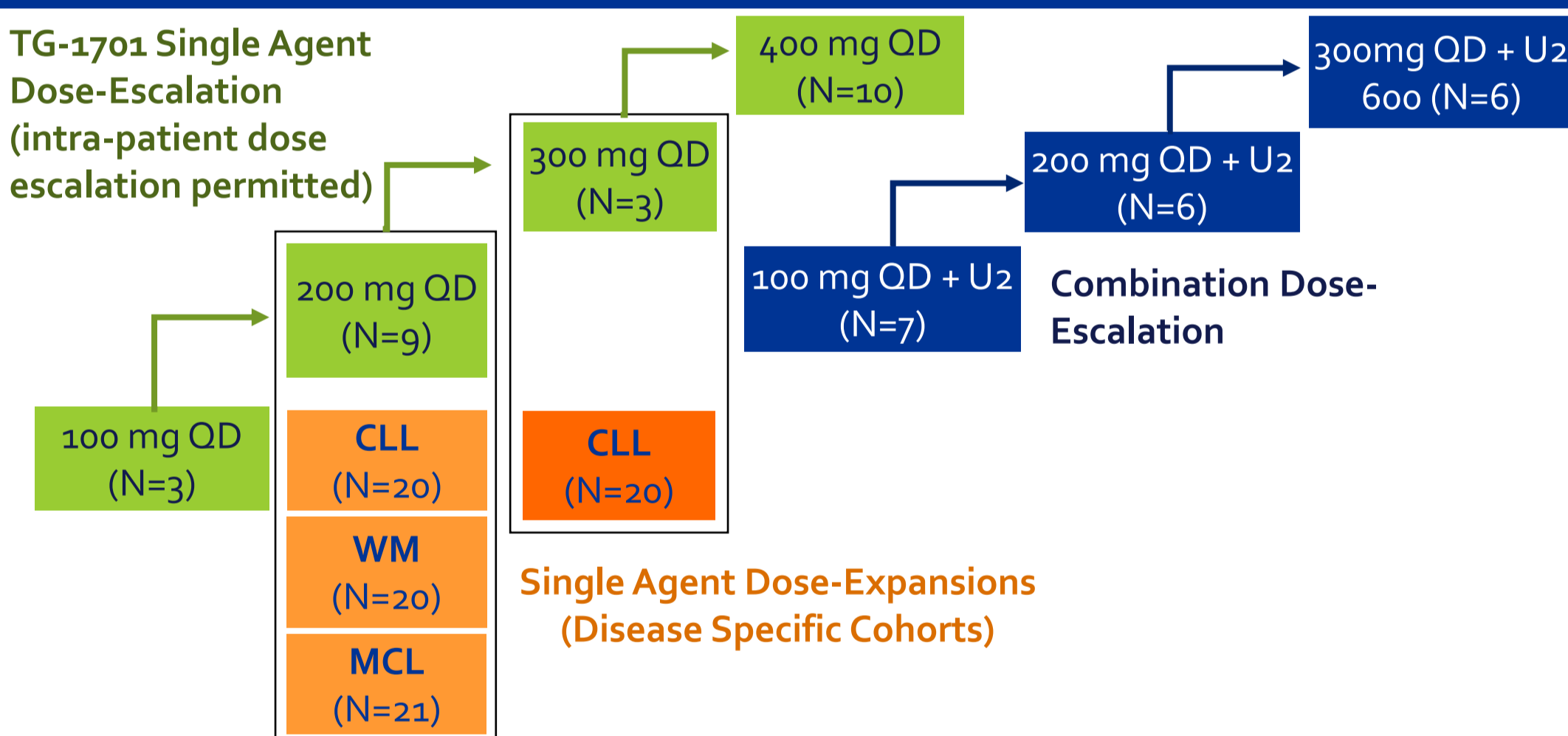
## Objectives

- 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 Eligibility Criteria

- R/R pts with histologically confirmed B-cell lymphoma or CLL warranting systemic therapy were included. Previously untreated pts could be enrolled if unsuitable for standard front-line chemoimmunotherapy, in the disease-specific cohorts
- Pts with prior therapy with a BTK inhibitor; any severe or uncontrolled illness or condition; concomitant warfarin therapy (other anticoagulation is allowed), were excluded

## Trial Design



- 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 D<sub>1</sub>, 8, 15 of C<sub>1</sub>, and D<sub>1</sub> of C<sub>2</sub> through C<sub>6</sub>, and D<sub>1</sub> every 3 C thereafter.

## RESULTS

### Patient Demographics and Disease Characteristics

Characteristic	Dose-escalation Phase		Disease-specific Cohorts			
	TG-1701 (N=25)	TG-1701 + U2 (N=19)	200 mg QD		300 mg QD	
			CLL (N=20)	WM (N=20)	MCL (N=21)	CLL (N=20)
Male sex N(%)	14 (56)	8 (42)	7 (35)	12 (60)	13 (62)	10 (50)
Age, years, median (min/max)	68 (49/86)	69 (47/81)	71 (53/87)	73 (57/92)	70 (57/85)	71 (49/78)
≥75 years N(%)	7 (28)	5 (26)	4 (20)	8 (40)	5 (24)	6 (30)
ECOG 0/1/2 (%)	56/44/0	79/21/0	35/65/0	45/50/5	48/48/4	35/65/0
Prior therapies, median (range)	1 (1-5)	2 (1-5)	1 (0-5)	1 (0-4)	3 (0-10)	1 (0-5)
Refractory to last prior therapy N(%)	7 (28)	3 (16)	2 (10)	3 (15)	4 (19)	1 (5)
Prev. anti-CD20 therapy N(%)	25 (100)	19 (100)	14 (93)*	12 (100)*	18 (100)*	14 (93)*
Treatment-naïve N(%)	-	-	5 (25)	8 (40)	3 (14)	4 (20)

\*Calculation excludes treatment-naïve patients

## Patient Disposition

Cutoff: Apr 30, 2021	Dose-escalation Phase		Disease-specific Cohorts	
	TG-1701 (N=25)	TG-1701 + U2 (N=19)	200 mg (N=61)	300 mg (N=20)
Ongoing treatment N(%)	18 (72)	16 (84)	45 (74)	18 (90)
Intra-pt dose escalation N(%)	7 (28)	-	-	-
Dose redn. (any agent) N(%)	4 (16)	5 (31)	2 (3)	1 (5)
Pts off study N(%)	7 (28)	3 (16)	16 (26)	2 (10)

### Reason for tx d/c N(%)

Reason for tx d/c N(%)	TG-1701 (N=25)	TG-1701 + U2 (N=19)	200 mg (N=61)	300 mg (N=20)
Progression by criteria	5 (20)	2 (11)	10 (16)	-
Clinical progression	-	-	1 (2)	-
Treatment-related AE	-	-	1 (2)	-
Non-treatment related AE	-	1 (5)	2 (3)	2 (10)
Pt / physician decision - Other	2 (8)	-	2 (3)	-

## Safety

### 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		CLL cohort (300 mg) N=20	
	Any Grade	Grade 3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Respiratory tract infection	9 (36)	2 (8)	6 (10)	-	2 (10)	-
Constipation	8 (32)	-	3 (5)	-	-	-
Bruising	7 (28)	-	5 (8)	-	-	-
Fatigue	5 (20)	-	2 (3)	-	1 (5)	-
Rash	4 (20)	1 (4)	3 (5)	-	1 (5)	-
Nausea	4 (16)	-	1 (2)	-	2 (10)	-
Dizziness	4 (16)	-	1 (2)	-	-	-
Headache	3 (12)	-	6 (10)	-	1 (5)	-
Diarrhea	3 (12)	-	7 (11)	-	2 (10)	-
Epistaxis	3 (12)	-	2 (3)	-	-	-
COVID-19	-	-	4 (7)	1 (2)	3 (15)	2 (10)

- Hematologic and lab abnormalities
- Neutropenia 6 (24) 2 (8) 8 (13) 5 (8) 2 (10) 2 (10)
- ALT increased 6 (24) 3 (12)<sup>a</sup> 5 (8) 1 (2) 3 (15) 1 (5)
- AST increased 5 (20) 1 (4) 3 (5) - 3 (15) 1 (5)
- Anemia 4 (16) - 7 (11) 3 (5) - -
- There have been no G<sub>4</sub> AEs in the dose escalation of monotherapy**
- At 200mg and 300 mg QD (n=81), AE's of special interest were G<sub>3</sub> hypertension 4.9% and atrial fibrillation 1.2%. There have been no instances of major bleeding**
- <sup>a</sup>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 Combo

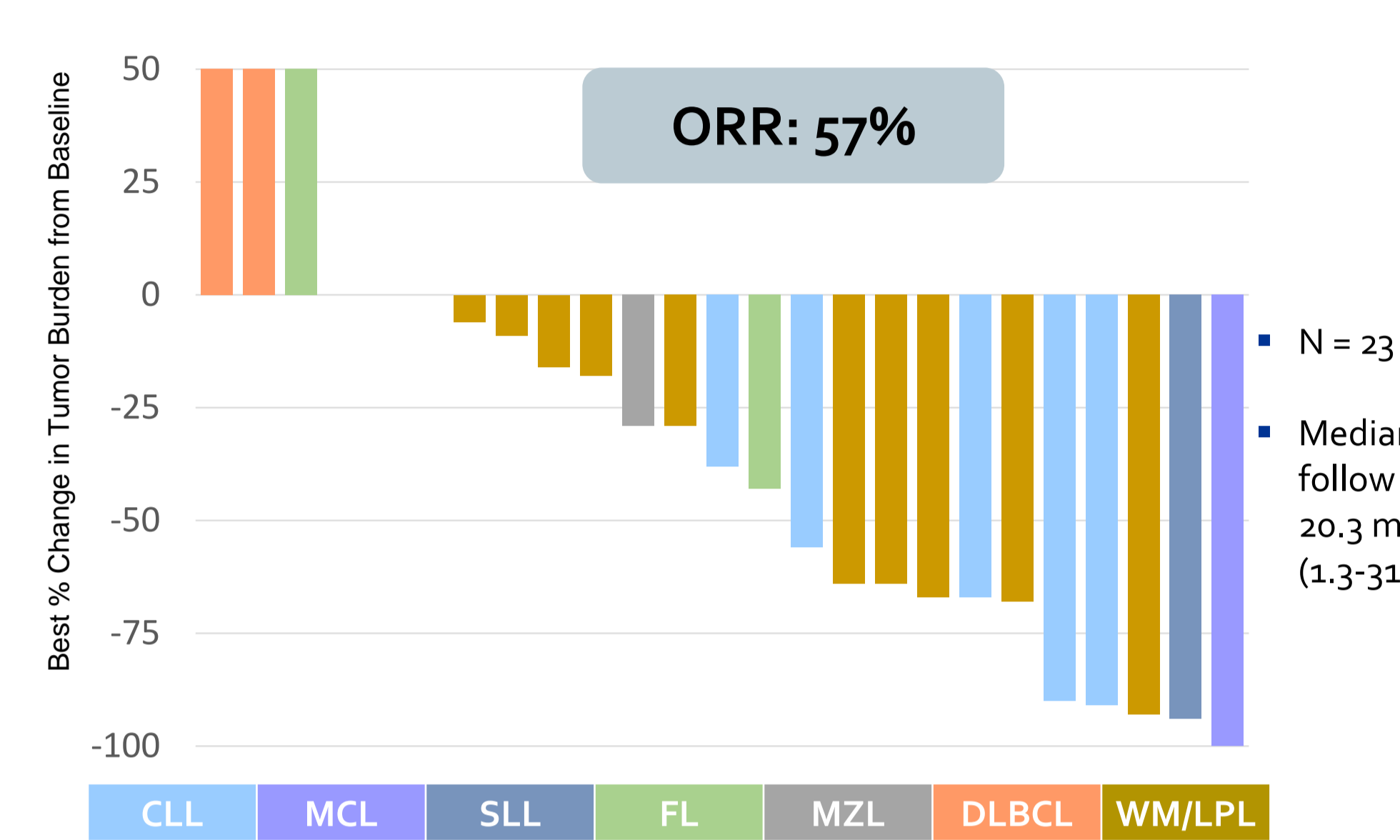
Adverse event, N(%)	Patients (N=19)		
	Any Grade	Grade 3	Grade 4
Diarrhea	9 (47)	2 (11)	-
IRR <sup>a</sup>	9 (47)	1 (5)	-
Bruising	9 (47)	-	-
Nausea	6 (32)	1 (5)	-
Hypertension	6 (32)	1 (5)	-
Fatigue	4 (21)	-	-
Rash	3 (16)	-	-
Vomiting	3 (16)	-	-

- <sup>a</sup>IRR: includes the terms "chest tightness", and "facial flushing"
- <sup>b</sup>All cases of G<sub>3</sub> 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.
- <sup>c</sup>The G<sub>4</sub> ALT increased was symptomatic (vomiting) and with abnormal liver function, the patient has recovered with complete response and remains on study therapy.

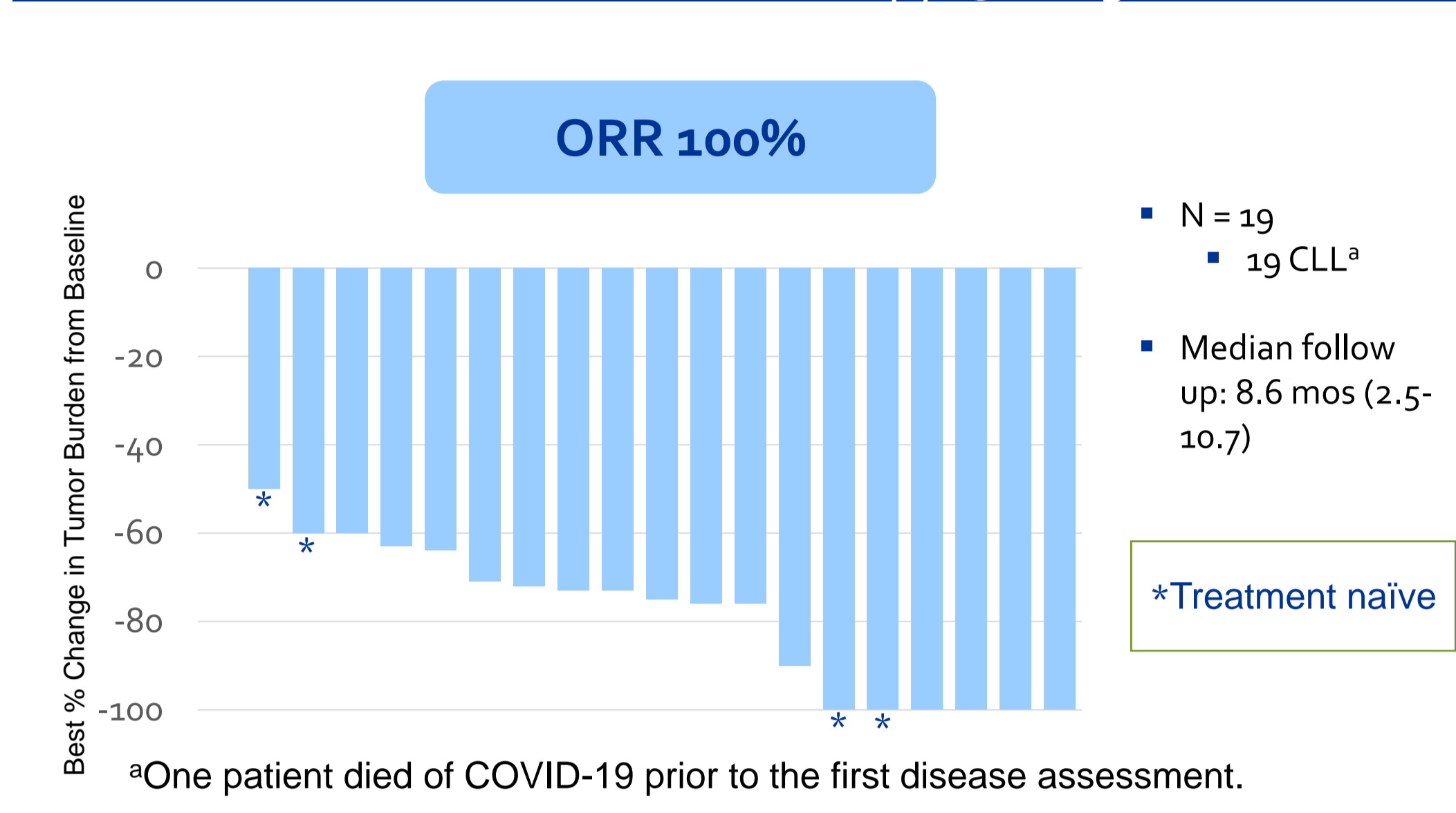
## RESULTS

### Efficacy

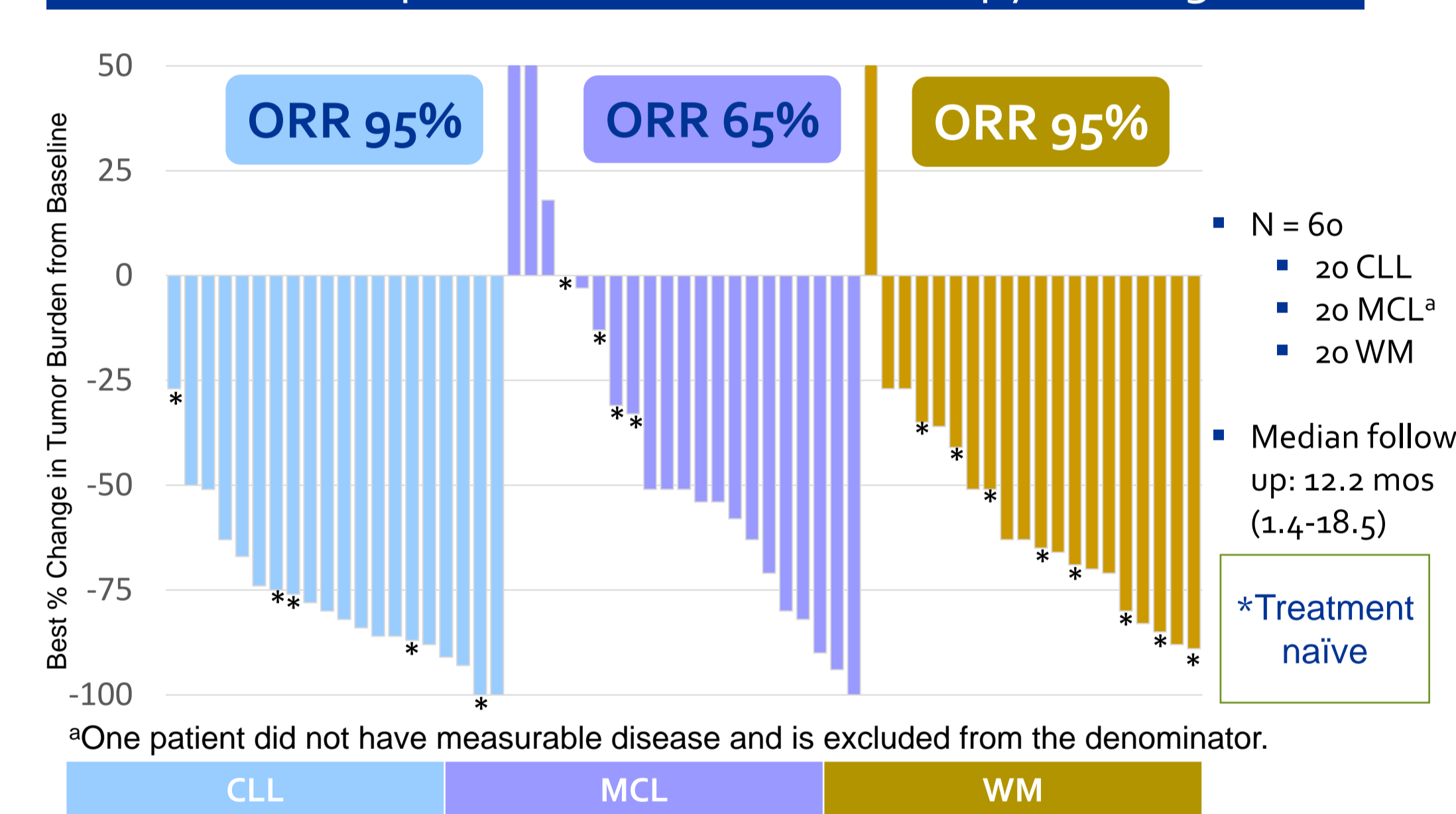
#### Dose-escalation (100 to 400 mg QD) Monotherapy



#### CLL Cohort Monotherapy (300mg)



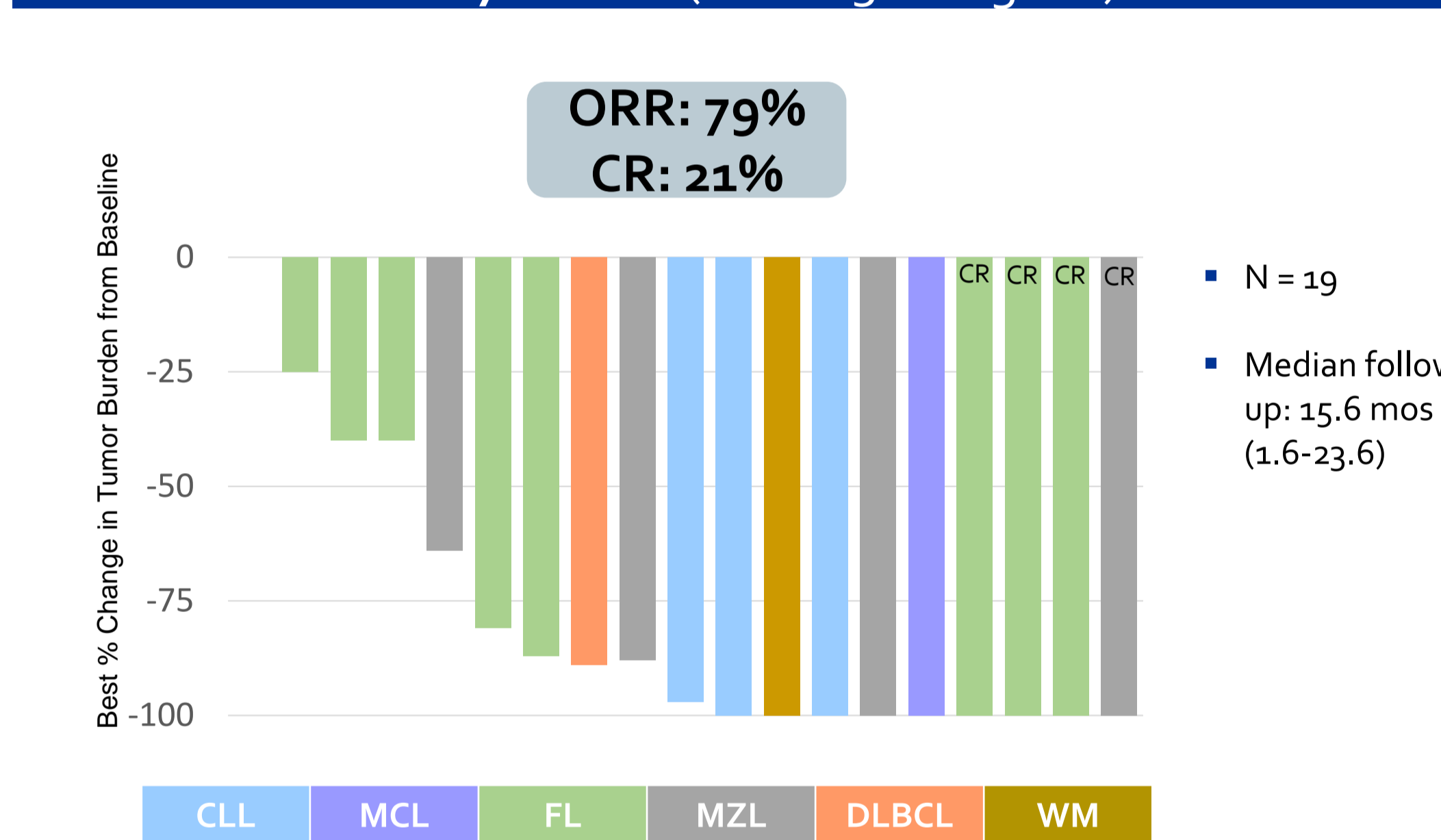
#### Disease-Specific Cohorts Monotherapy (200mg)



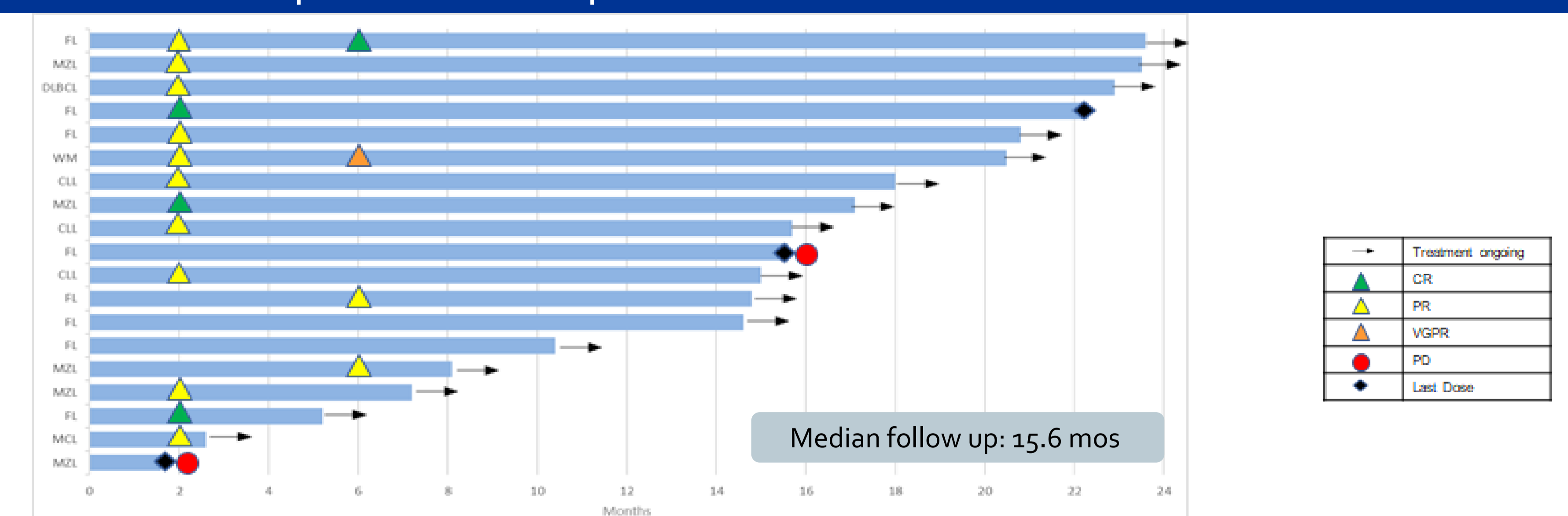
<sup>a</sup>One patient did not have measurable disease and is excluded from the denominator.

Note: Waterfall plots include all patients with measurable disease at baseline and at least one evaluable post-baseline scan

#### TG-1701 + U2 (100 to 300 mg QD)



## Treatment Exposure and Response Duration Dose Escalation Combination Therapy



## SUMMARY

- 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.