

UBLITUXIMAB (TG-1101), A NOVEL ANTI-CD20 MONOCLONAL ANTIBODY FOR RITUXIMAB RELAPSED/REFRACTORY B-CELL MALIGNANCIES

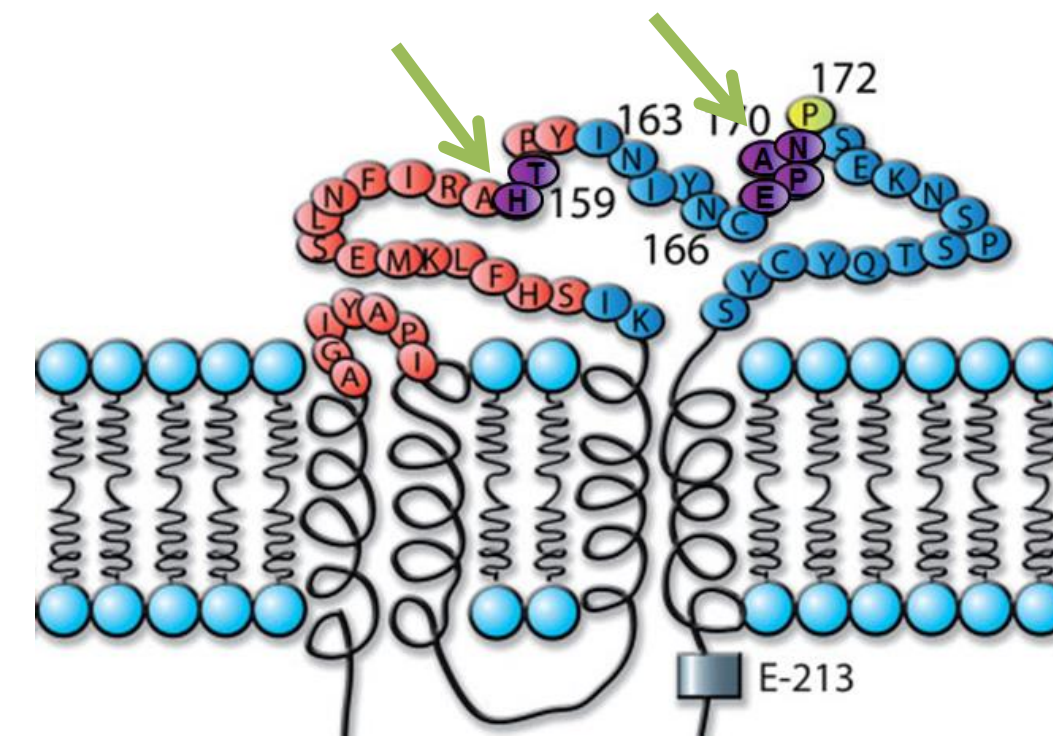
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BACKGROUND

Ublituximab (TG-1101) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen. Ublituximab has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors and therefore demonstrates greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels. A completed Phase I trial of single agent ublituximab in patients with relapsed/refractory CLL reported a response rate of 45% (EHA 2013). Two clinical studies (Phase I/II and Phase I) were completed with ublituximab in patients with rituximab relapsed and refractory B-cell lymphoma (NHL and CLL). TG-1101-101 is a study of single agent ublituximab in this patient population, while TG-1101-102 is a study of ublituximab administered in combination with lenalidomide, an immunomodulating agent that has displayed activity in lymphoma and has been shown to enhance the ADCC activity of anti-CD20 antibodies. Herein we report on the clinical results of both studies.

UBLITUXIMAB



Ublituximab, a next generation anti-CD20 antibody currently in clinical development, is characterized by a specific glycosylation pattern containing a high percentage of non-fucosylated antibody molecules at the Fc site. This specific pattern of glycosylation increases the affinity of antibodies for human FcγRIIIa (CD16), resulting in an increased antibody dependent cell-mediated cytotoxicity (ADCC) by human FcγRIIIa-expressing effector cells.

Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

TG-1101-101: Single Agent Ublituximab in Rituximab Relapsed and Refractory NHL and CLL

STUDY DESIGN

Study TG-1101-101 (NCT01647971) is a Phase I/II trial currently closed to enrollment with patients ongoing. The study endpoints are as follows:

- **Primary:** Safety and Maximum Tolerated Dose (MTD)
- **Secondary:** ORR (CR + PR), Pharmacokinetics (PK) and PFS

Phase I Cohort Design: 3 + 3 dose-escalation design of 4 cohorts

Cohort 1	Cohort 2	Cohort 3	Cohort 4
450 mg	600 mg	900 mg	1200 mg

Cohort Expansion: NHL (900 & 1200 mg) / CLL (600 & 900 mg)

Induction NHL: ublituximab administered wkly x 4 in Cycle 1 (cycle=28 days)

Induction CLL: ublituximab administered Days 1, 8, 15 of Cycles 1 & 2

Maintenance: monthly infusions for patients with SD or better response starting Cycle 3, and infusions every 3 months starting Cycle 6

Key Inclusion Criteria

- Relapsed or refractory to prior RTX-based regimen (refractory = PD on or within 6 months of RTX; relapsed = PD > 6 months after RTX)
- B-cell Lymphoma (NHL & CLL) with measurable / evaluable disease
- ECOG ≤ 2, No Hepatitis B/C or HIV
- Adequate organ / marrow function with baseline ANC ≥ 1,000 cells/μL and platelets ≥ 50k/μL.

DEMOGRAPHICS

Evaluable for Safety:	35	18 Female / 17 Male		
Evaluable for Efficacy[†]:	30	Median Age: 66 (range 45 – 88)		
Type of B-cell Lymphoma (n)				
Indolent NHL (20)	CLL/SLL (8)		Aggressive NHL (7)	
Follicular (12)	CLL (8)		Mantle Cell (5)	
Marginal Zone (8)			DLBCL (2)	
Demographic	All Pts	iNHL	CLL	aNHL
ECOG 0/1/2 (n)	13 / 20 / 2	9 / 11 / 0	2 / 5 / 1	2 / 4 / 1
Median Prior Therapies: n (range)	3 (1 – 9)	3 (1 – 6)	3 (1 – 6)	2 (1 – 9)
≥ 4 Prior Therapies: n (%)	12 (34)	7 (35)	3 (38)	2 (29)
≥ 2 Prior Rituximab Regimens: n (%)	25 (71)	15 (75)	5 (63)	5 (71)
Refractory to Prior Treatment: n (%)	15 (43)	11 (55)	2 (25)	2 (29)
Refractory to Prior Rituximab: n (%)	15 (43)	12 (60)	1 (13)	2 (29)

[†]5 pts not evaluable: 4 patients off study prior to first efficacy assessment (2 for non-related AE, 1 for SAE, 1 withdrew consent), 1 too early to evaluate

RESULTS

Safety

Among the 12 patients treated in the dose-escalation Phase I and the 23 patients in the expansion cohorts to date, no DLTs were observed, and no MTD was reached. Adverse events (CTCAE v 4.0) are summarized as follows:

At Least Possibly Related AE's Occurring in > 5% of Pts (n=35)

AE	All Patients (n = 35)	
	All Grades n (%)	Grade 3/4 n (%)
Infusion Reaction*	10 (29%)	0
Fatigue	5 (14%)	1 (3%)
Diarrhea	4 (11%)	0
Pain (General)	4 (11%)	0
Dysgeusia	3 (9%)	0
Bilirubin Increase	2 (6%)	0
Pruritus	2 (6%)	0

*IRR also includes chills, itching, dyspnea, throat irritation

4 CLL / 6 NHL pts had IRR's

- 6 pts had IRR's on the Day 1 infusion only
- IRR's were manageable with infusion interruptions and recovered w/o sequelae
- Patients received all scheduled infusions

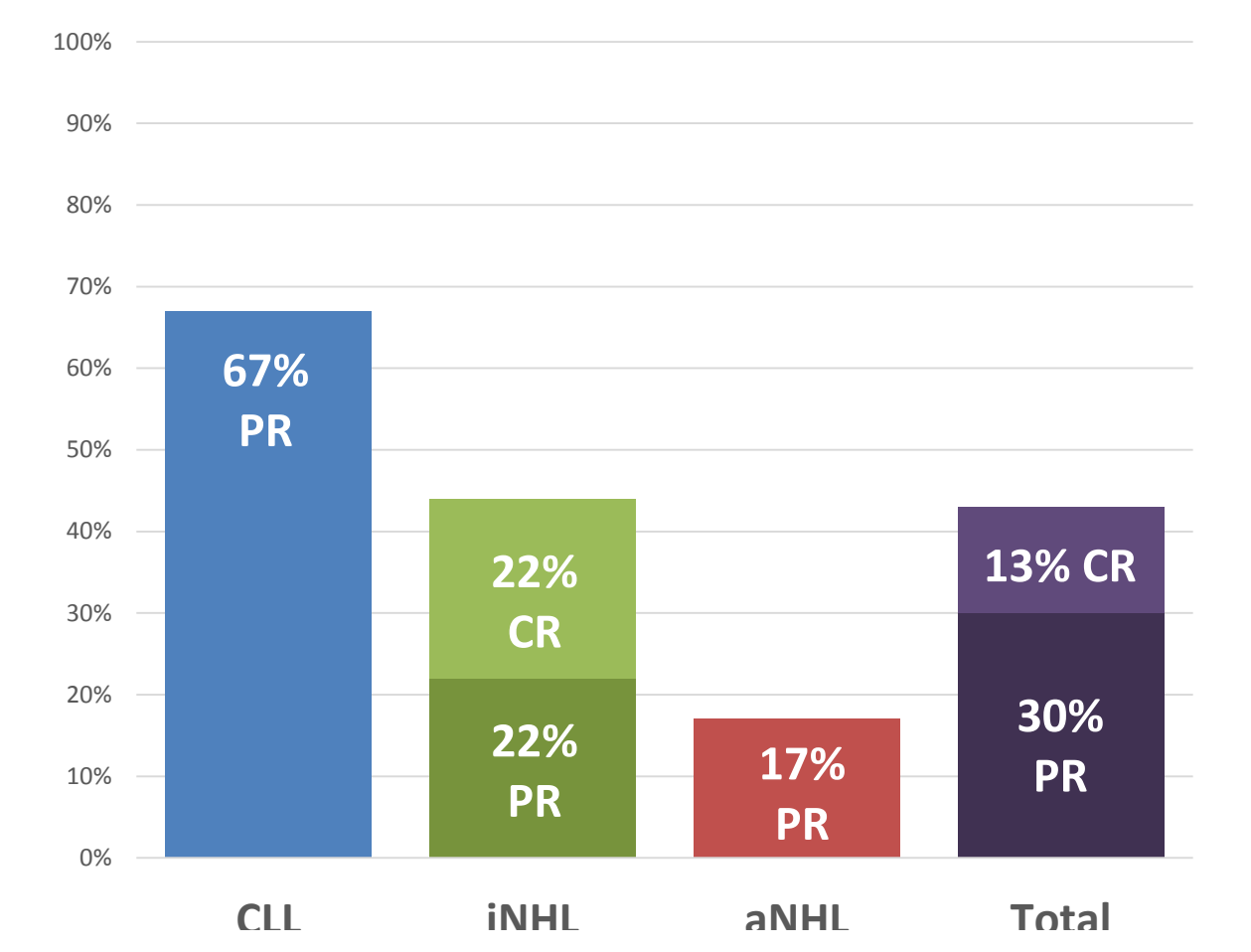
Infusion times decreased to an average of 90 minutes for the 4th and all subsequent infusions

Lab Abnormalities at Least Possibly Related

AE	CLL (n=8)		NHL (n=27)	
	Gr 1/2 n	Gr 3/4 n	Gr 1/2 n	Gr 3/4 n
Neutropenia	1	3	0	0
Thrombocytopenia	1	1	0	0
Anemia	0	0	0	1

Efficacy

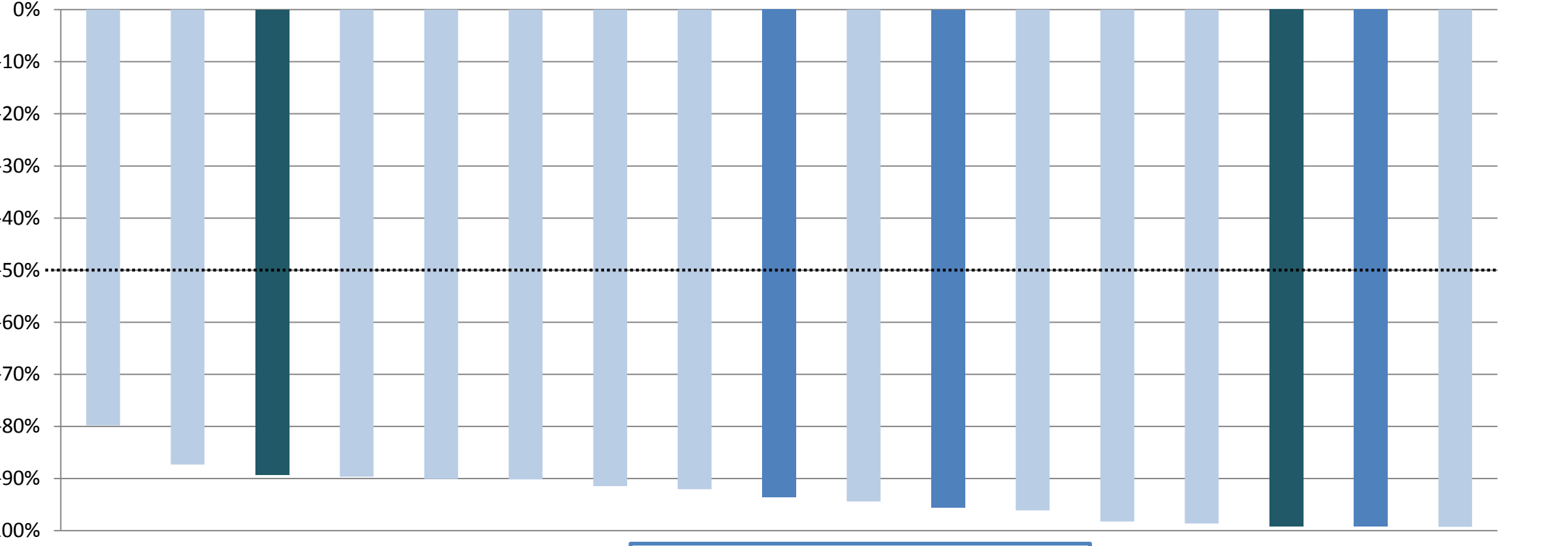
Overall Response by Lymphoma Sub-type



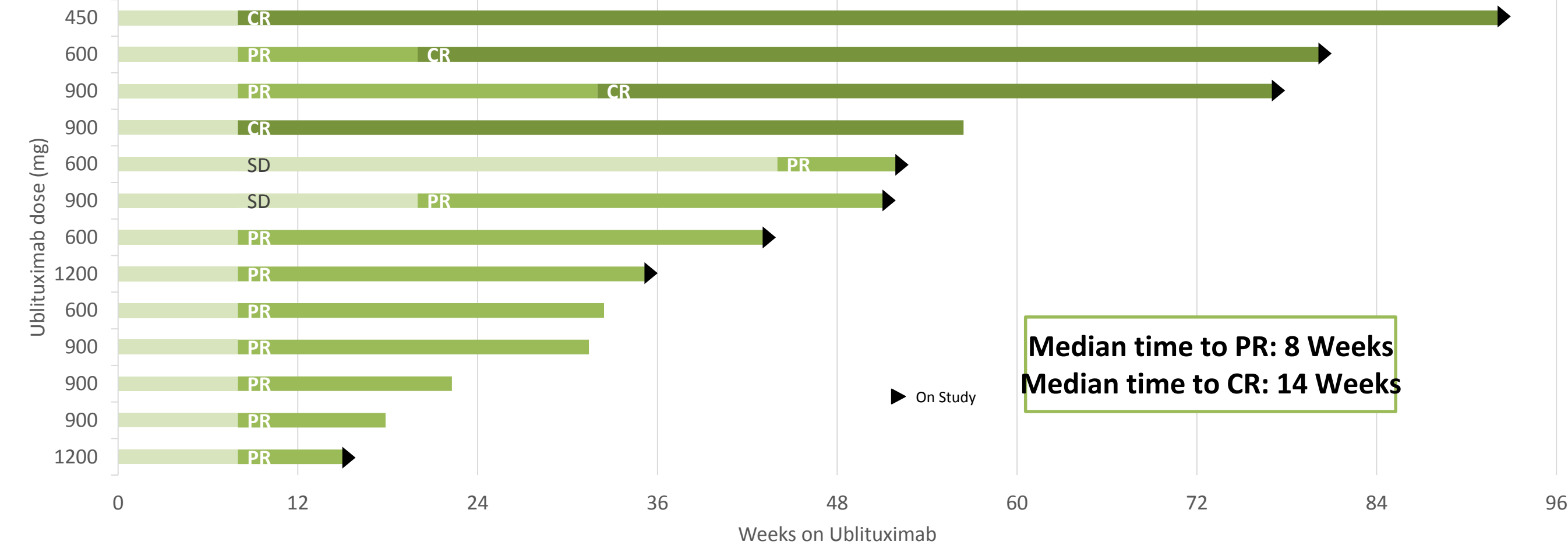
Type	Pts (n)	CR n (%)	PR n (%)	ORR n (%)
CLL	6	-	4 (67)	4 (67)
FL	12	2 (17)	2 (17)	4 (33)
MZL	6	2 (33)	2 (33)	4 (67)
MCL	5	-	-	-
DLBCL	1	-	1 (100)	1 (100)
Total	30	4 (13)	9 (30)	13 (43)

% Change in ALC at First Efficacy Assessment

Meta-analysis of CLL pts from current and past studies on single agent UTX



Evolving Responses for Patients on Maintenance Ublituximab



Median Progression Free Survival (PFS) for patients who achieved ≥ Stable Disease (SD) as best response has not been reached, with median PFS for all study patients at 34 weeks. 14/30 patients have not progressed with 12 patients remaining on study treatment (longest patient on study treatment is 21+ months).

CONCLUSIONS TG-1101-101

- Ublituximab is well tolerated even at the highest dose levels tested, with no DLT's observed and no MTD reached. Safety profile supports combination therapy.
- Day 1 IRR's are the most frequent AE (G 1/2 only). G 3/4 events have been limited. Infusion times declined to an average of 90 minutes for the 4th and subsequent infusions
- Significant single agent activity observed in patients with rituximab relapsed/refractory CLL and iNHL
- Rapid and profound lymphocyte depletion observed in CLL patients (median time to >50% reduction of 1 day)
- Responses have been durable (patients in response >1 year on single agent ublituximab) with some improving in response over time with continued ublituximab maintenance
- Studies of ublituximab in combination with PI3K delta and BTK inhibitors are ongoing. Phase III studies in B-cell malignancies are currently in development

TG-1101-102: Ublituximab + Lenalidomide in Rituximab Relapsed and Refractory NHL and CLL

STUDY DESIGN

Key Inclusion Criteria

- Relapsed or Refractory B-cell NHL or CLL/SLL following at least one prior line of anti-CD20 therapy
- Measurable / evaluable disease; ECOG ≤ 2
- Adequate organ / marrow function with baseline ANC ≥ 1,000 cells/μL and platelets ≥ 50k/μL.

Dose Escalation Schema

Cohort	Patients	Ublituximab	Lenalidomide
1	3 – 6	450 mg	10 mg
2	3 – 6	450 mg	15 mg
3	3 – 6	600 mg	10 mg*
4	3 – 6	900 mg	10 mg*

*Lenalidomide dose titrated per patient tolerability

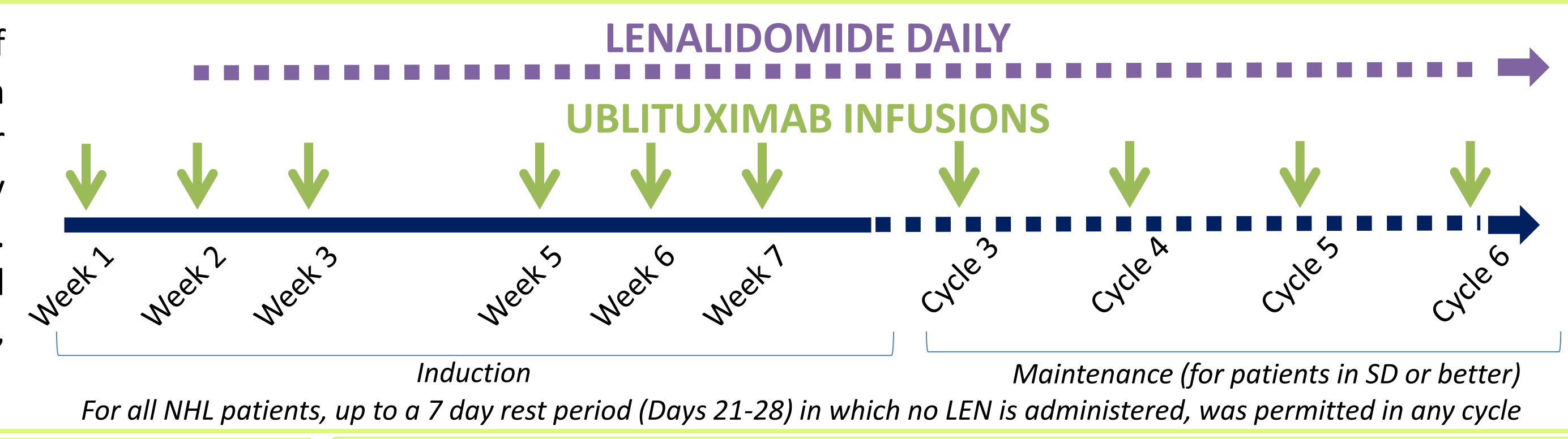
- As CLL and NHL patients tolerability vary, the protocol was amended during Cohort 2 to allow a revised administration schedule for lenalidomide in which patients would start at 10 mg QD, and titrate dose in 5 mg increments per cycle based on individual tolerability.

Demographics

Evaluable for Safety:	10	7 Male / 3 Female		
Evaluable for Efficacy[†]:	9	Median Age: 66 (range 47 – 76)		
ECOG 0/1:	2/8	Median Prior Therapies: 3 (range 3-6)		
Refractory to Prior Tx: 90%	Rituximab Refractory: 70%			
Prior R-Benda: 90%	Prior BTK/PI3K: 30%	≥ 2 Prior Rituxan: 100%		
Lymphoma Subtype				
CLL/SLL: 5	Follicular: 1	Mantle Cell: 3	Burkitt's: 1	

[†]1 patient not evaluable due to non-related SAE

Dosing Schedule



Induction (for all NHL patients, up to a 7 day rest period (Days 21-28) in which no LEN is administered, was permitted in any cycle)

Maintenance (for patients in SD or better)

Safety

Adverse Event	Total AE's All Grades	Related AE's Occurring in ≥ 2 patients (n = 10)			
		UTX Related		LEN Related	
		G 1/2 n	G 3/4 n	G 1/2 n	G 3/4 n
Infusion Reaction	6	5	1	0	0
Neutropenia	5	0	2 [†]	1	4 [†]
Diarrhea	4	0	0	4	0
Constipation	3	0	0	3	0
Fatigue	3	2 [†]	0	3 [†]	0
Nausea	4	1	0	3	0
Anemia	2	0	1 [†]	1	1 [†]
Hoarseness	2	1	0	1	0
Rash	2	0	0	2	0
Tumor Flare	2	0	0	2	0

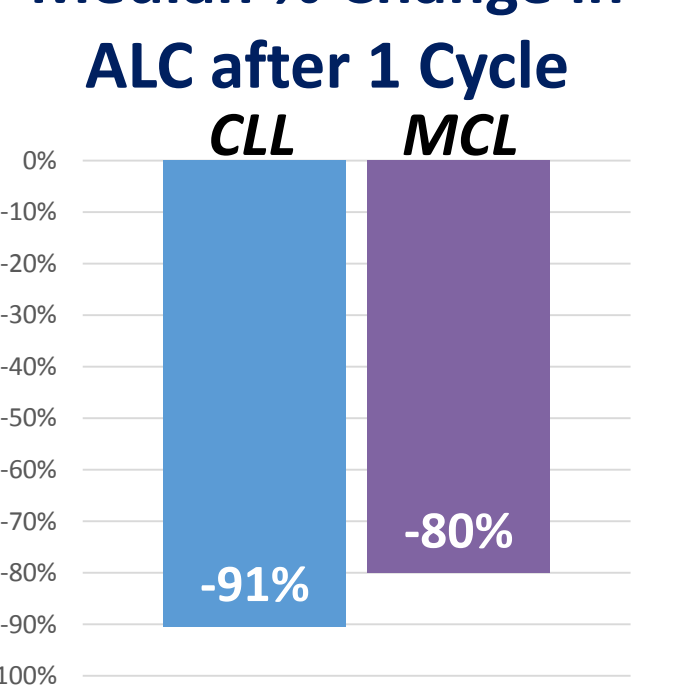
[†]Causality of some events were attributed to both UTX and LEN

- 3 patients had their LEN dose reduced or withdrawn (2 neutropenia, 1 nausea); 1 had their UTX dose reduced due to neutropenia.
- Although no DLT's were reported, dose interruptions or reductions occurred in 6/10 patients while on study.

Efficacy

- 2/9 patients achieved a PR while 2 additional patients (CLL) achieved SD > 6 months.
 - 1 PR in a MCL patient refractory to idelalisib and rituximab
 - 1 PR in a patient with rituximab refractory FL.
- Lymphocyte depletion was rapid and profound with > 90% reduction in CLL and 80% reduction in MCL after 1 cycle (3 infusions of UTX)

Median % Change in ALC after 1 Cycle



CONCLUSIONS TG-1101-102

- The combination of UTX+LEN was explored in a heavily pre-treated pt. population (70% RTX refractory, 30% BTK/PI3Kδ refractory)
- The majority of AE's observed were G 1/2 in severity and managed by dose reductions and delays, and a titrating regimen for LEN
- A >90% median reduction in ALC was observed in heavily refractory patients with CLL following 1 Cycle of therapy
- Responses were observed in patients refractory to rituximab and the PI3Kδ inhibitor, idelalisib