Tolerability and activity of chemo-free triplet combination of umbralisib (TGR-1202), ublituximab, and ibrutinib in patients with advanced CLL and NHL

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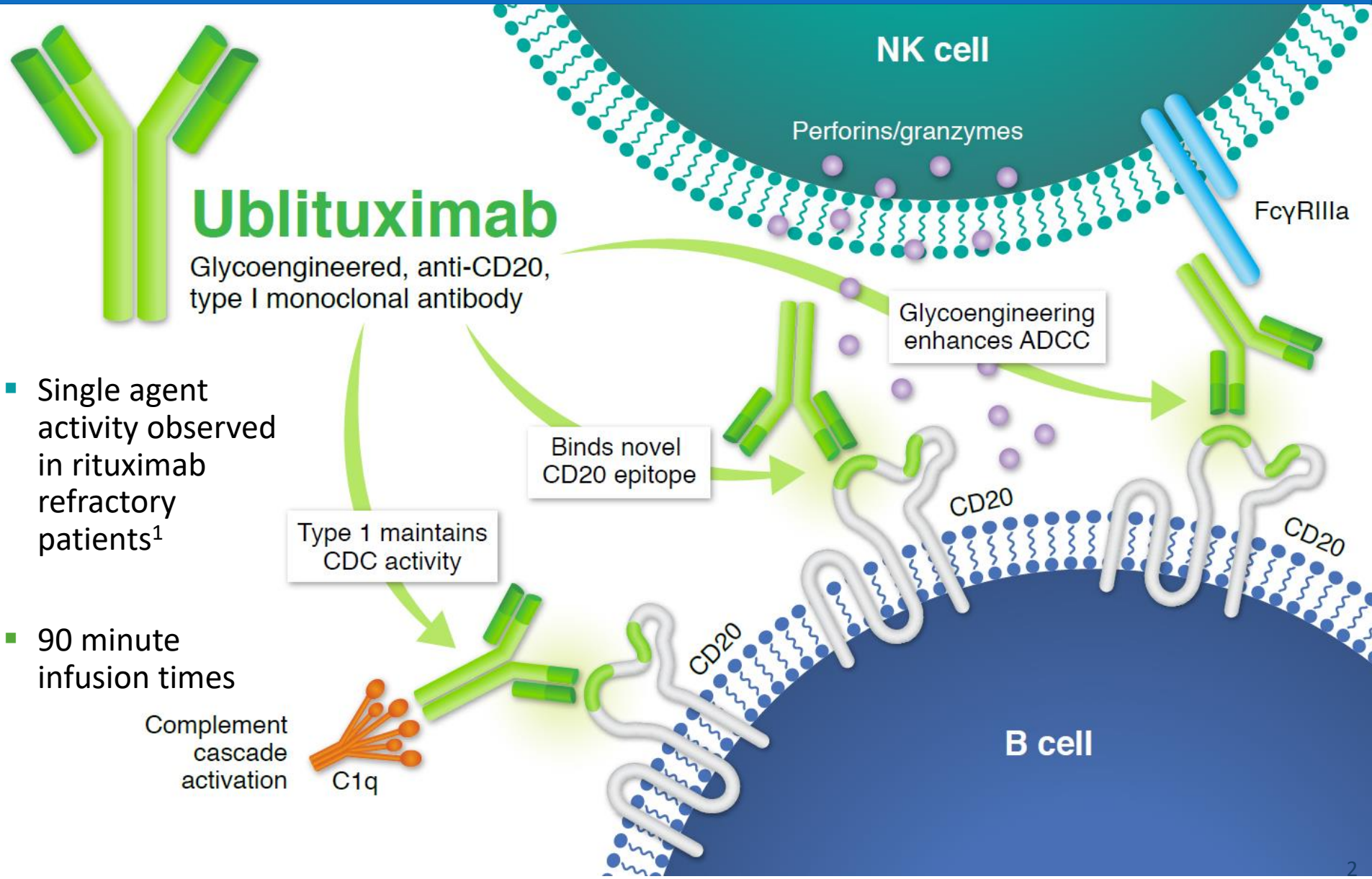
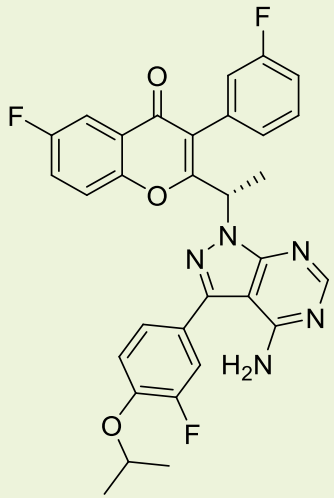
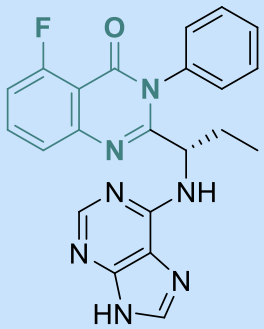
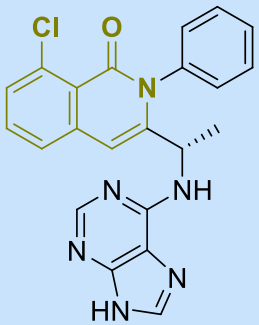
Ublituximab

- Single agent activity observed in rituximab refractory patients[1]
- 90 minute infusion times



Umbralisib (TGR-1202)

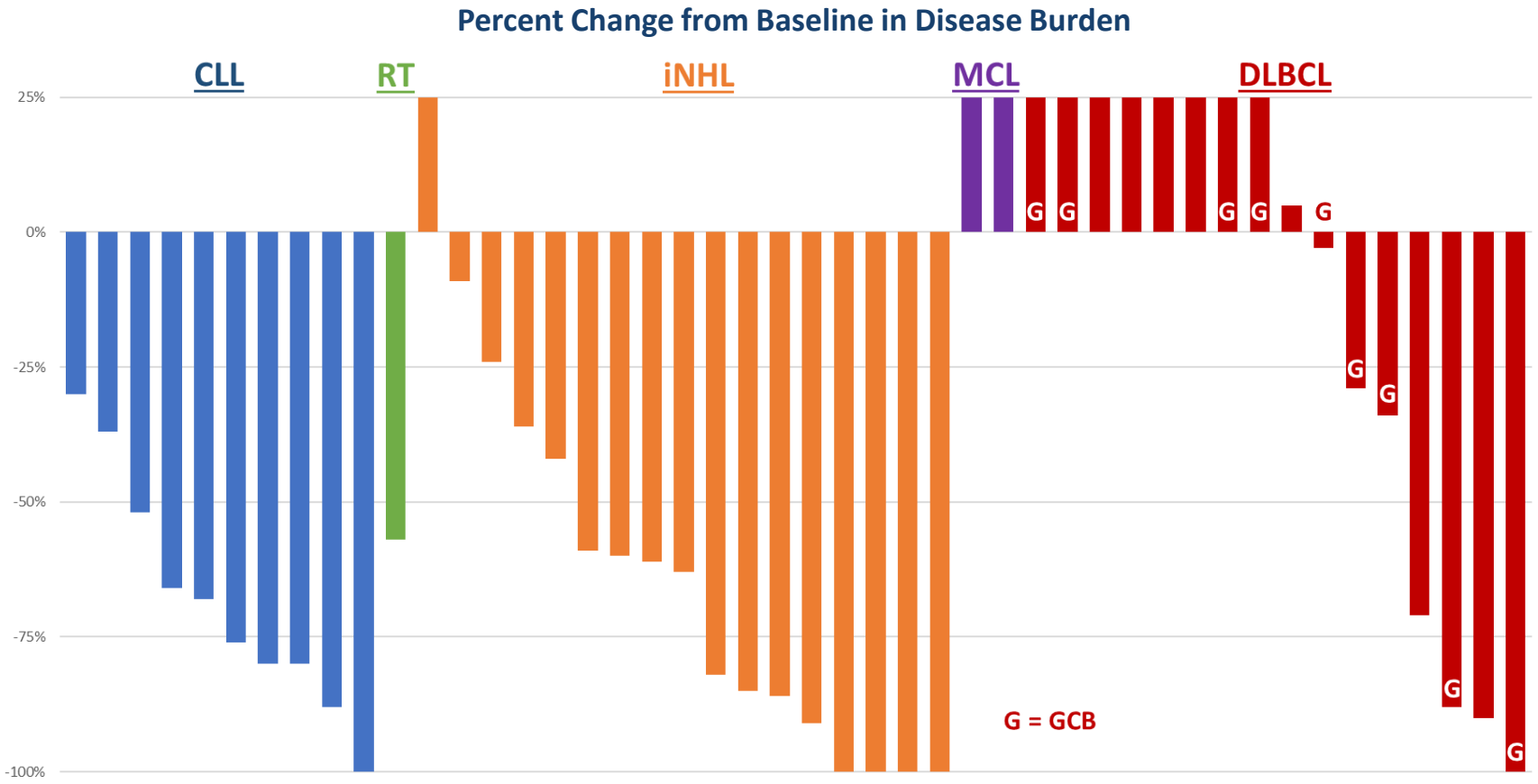
- Next generation PI3Kδ inhibitor, with a unique structure and improved tolerability

Umbralisib (TGR-1202)	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

Burris et al, ASCO 2015

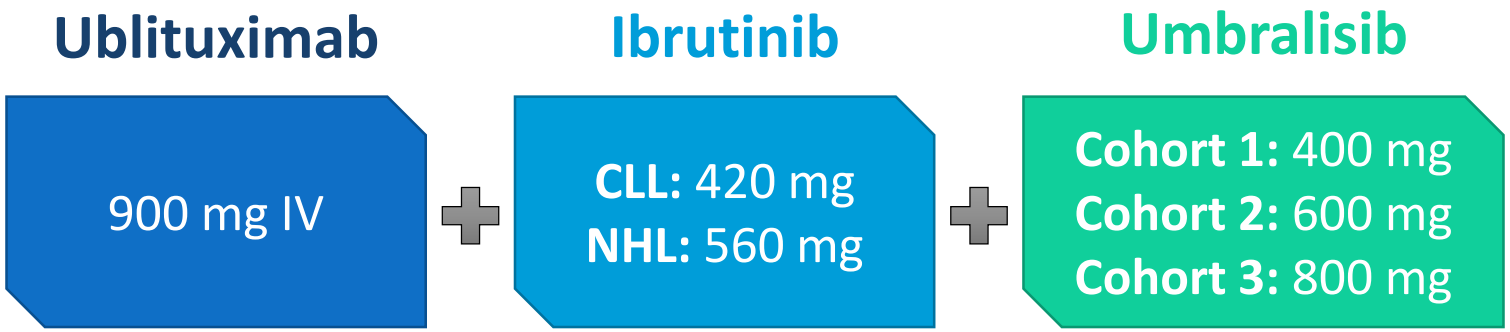
Ublituximab + Umbralisib (TGR-1202)

- Active combination regimen currently in registration directed studies for CLL (UNITY-CLL) and NHL (UNITY-NHL)



Lunning et al, ASH 2015

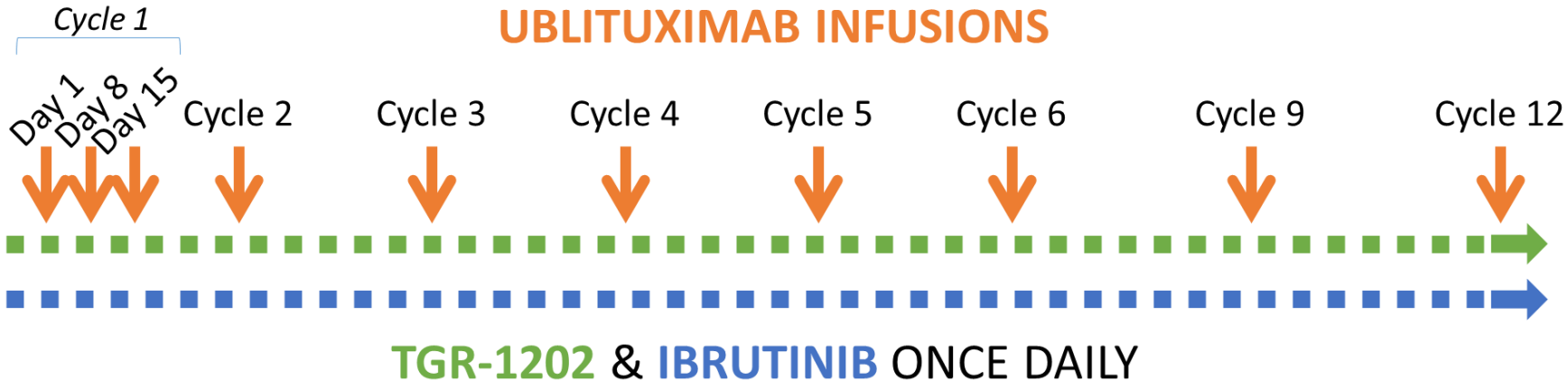
Study Design



- Enrolling patients with CLL (naïve & previously treated) and NHL (relapsed or refractory only)
- 3 + 3 dose escalation design (CLL and NHL independently)
- No limit on prior # of therapies
- ECOG Performance Status ≤ 2
- ANC ≥ 500/µL; platelets ≥ 30 K/µL
- Patients with Richter's Transformation, or refractory to prior PI3Kδ inhibitors or prior BTK inhibitors are eligible

Study Design

- Both ibrutinib and TGR-1202 were administered QD starting on Day 1
- Efficacy assessed at Week 8 and every 12 weeks thereafter
- After Month 12, all patients remain on TGR-1202 and ibrutinib once-daily



Demographics

Evaluable for Safety (n)	38	
Evaluable for Efficacy† (n)	36	
Median Age, years (range)	65 (32 – 85)	
Male/Female	29/9	
Histology	**CLL/SLL**	20
	DLBCL	6
	FL	6
	MCL	4
	MZL	2
ECOG, 0/1/2	14/21/3	
Prior Therapy Regimens, median (range)	3 (0 – 6)	
Patients with ≥ 3 Prior Therapies, n (%)	21 (55%)	
Refractory to Prior Therapy, n (%)	13 (34%)	
Refractory to Rituximab, n (%)	15 (39%)	

†2 patients discontinued prior to first efficacy assessment (1 Pneumonia, 1 Investigator Discretion)

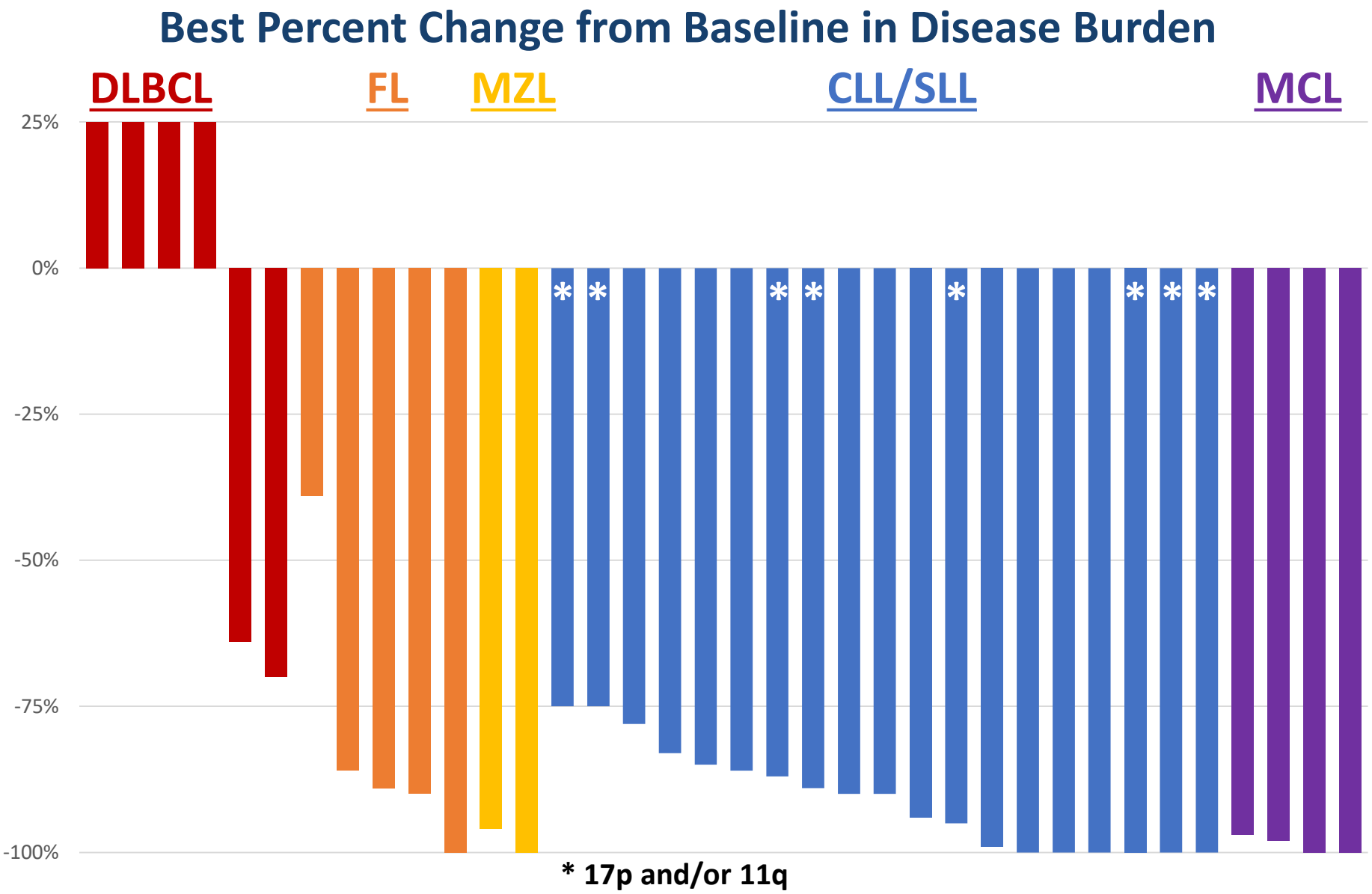
- 3 CLL patients were treatment naïve, all other patients were relapsed or refractory to prior therapy

Safety

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	18	47%	1	3%
Fatigue	18	47%	-	-
Dizziness	14	37%	1	3%
Insomnia	13	34%	-	-
Nausea	13	34%	-	-
Neutropenia	12	32%	7	18%
Cough	12	32%	-	-
Infusion related reaction	12	32%	-	-
Thrombocytopenia	11	29%	3	8%
Pyrexia	11	29%	1	3%
Rash	11	29%	1	3%
Anemia	10	26%	1	3%
Sinusitis	9	24%	-	-
Dyspnea	8	21%	1	3%
Stomatitis	8	21%	1	3%

- 1 DLT (reactivated varicella zoster) occurred CLL cohort level 1. No other DLT's were observed.
- Diarrhea majority Gr. 1 (32%) and Gr. 2 (13%), with no Gr. 4 event reported.
- Pneumonia (11% Gr. 3/4) and neutropenia were the only Gr. 3/4 AE's in >10% of patients
- Two patients discontinued due to an AE (sepsis and pneumonia)
- Median time on study 11.1 months (range 0.4 – 30+ months)

Efficacy: Waterfall Plot



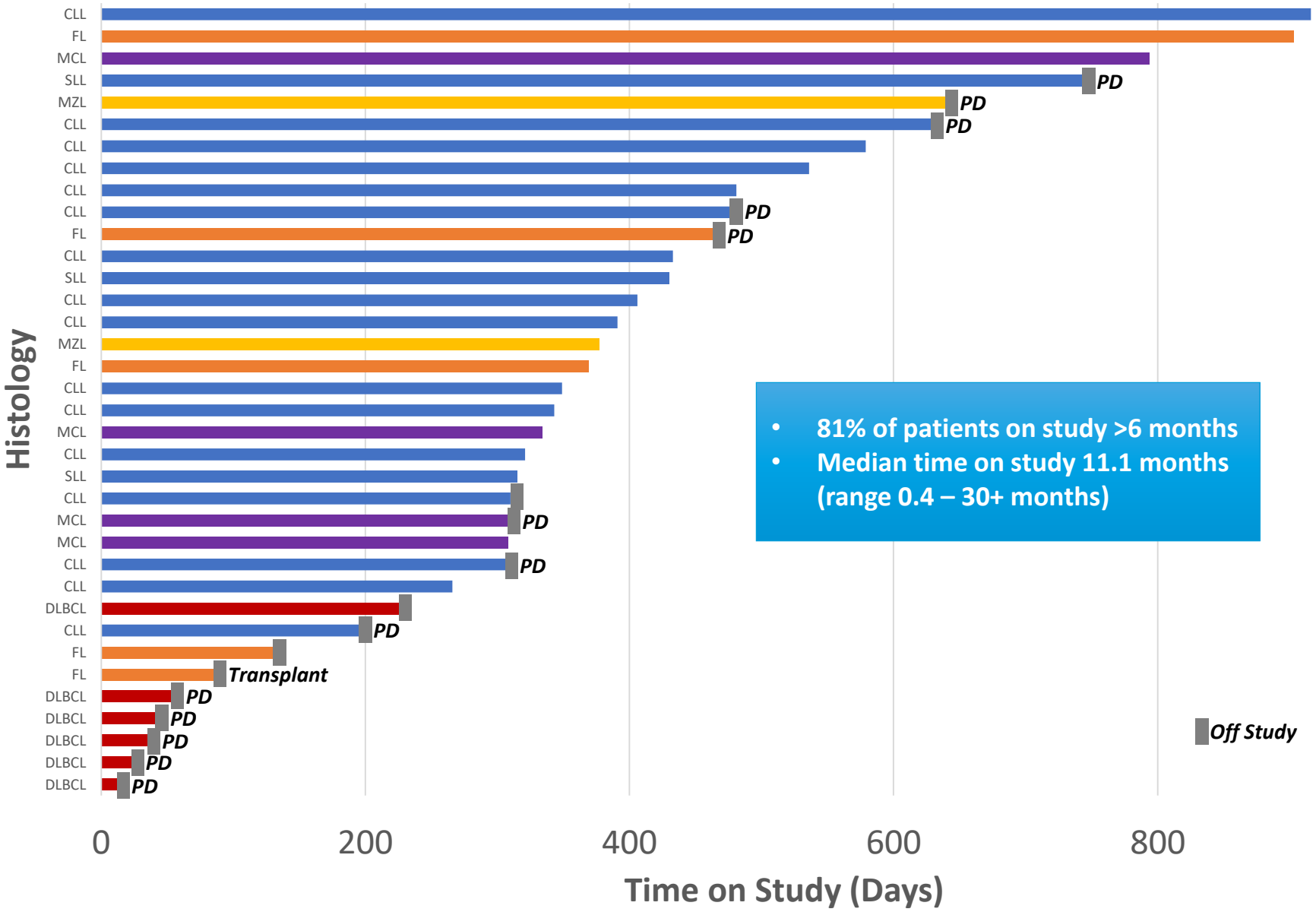
Efficacy: Overall Response Rate

Type	Pts (n)	CR† (n)	PR (n)	ORR n (%)	SD (n)	PD (n)
CLL/SLL	19	6	13	19 (100%)	-	-
MZL	2	1	1	2 (100%)	-	-
MCL	4	2	2	4 (100%)	-	-
FL	5	1	3	4 (80%)	1	-
DLBCL	6	-	1	1 (17%)	-	5
Total	**36**	**10**	**20**	**30 (83%)**	**1**	**5**

†CLL: 4/6 CR's pending bone marrow confirmation

- CLL
  - 8/16 (50%) had 17p and/or 11q deletion
  - All 3 treatment naïve patients achieved a PR
  - 3 had a prior BTK and/or PI3Kδ inhibitor, including one patient refractory to both idelalisib and ibrutinib (ongoing CR, 1.5+ years)
- FL patients were heavily pretreated including 2 with prior ASCT, 1 refractory to prior ibrutinib, and 1 with 5 prior lines of rituximab based therapy
- DLBCL
  - Median of 4 prior therapies
  - 4/6 were of non-GCB subtype, including the sole responder

Efficacy: Time on Study



- 81% of patients on study >6 months
- Median time on study 11.1 months (range 0.4 – 30+ months)

Conclusions

- With a median follow up of 11.1 months, the combination of ublituximab, umbralisib (TGR-1202), and ibrutinib appears to be well tolerated and demonstrates favorable efficacy in advanced CLL and NHL.
- The safety profile of this novel combination was favorable suggesting that TGR-1202 may be safely combined with targeted agents to overcome mechanisms of resistance.
- Many patients continue on therapy, with approximately half beyond 1 year and are experiencing a manageable safety profile.

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