Ublituximab, a Novel Glycoengineered Anti-CD20 mAb, In Combination with TGR-1202, a Next Generation Once Daily PI3Kδ Inhibitor, Demonstrates Activity in Heavily Pre-Treated and High-Risk Chronic Lymphocytic Leukemia and B-Cell Lymphoma

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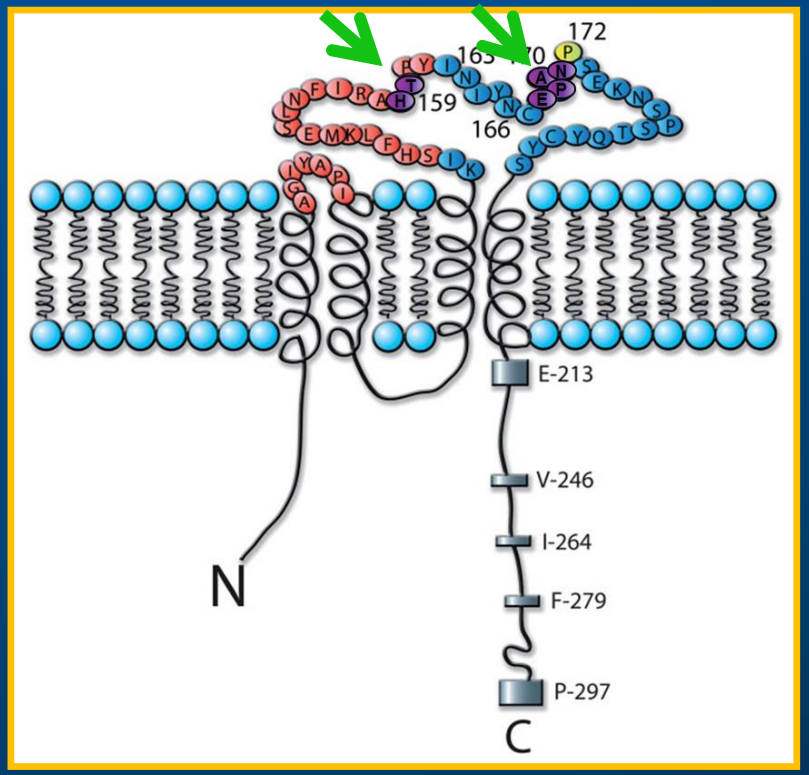
Ublituximab: Glycoengineered Anti-CD20 mAb

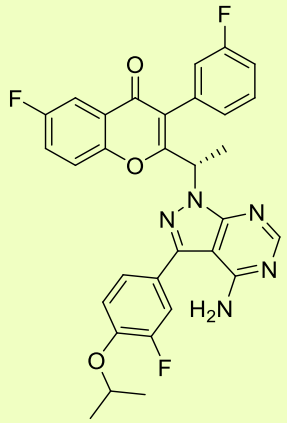
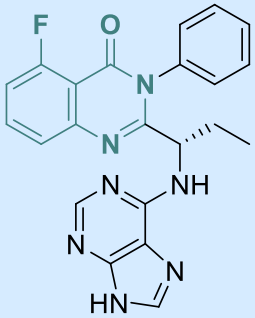
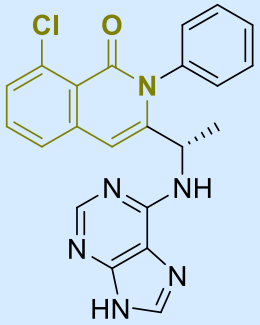
- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20
  (Green arrows in figure)
- Potential advantages over current standards of care:
  - Glycoengineered for enhanced ADCC
  - Demonstrated activity in “low” CD20 expressing cell lines:
    - CLL/SLL
    - Refractory B-NHL
  - Single agent responses observed in rituximab refractory patients[1]



(1) O’Connor et al, ASCO 2014

Source: Adapted from Ruuls et al 2008

TGR-1202: Novel PI3Kδ (delta) Inhibitor

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

- PK profile that allows once-daily oral dosing
- Absence of hepatic toxicity in rel/ref hematologic malignances[1]
- 93% nodal PR rate in patients with rel/ref CLL[1]
- Dose escalation ongoing—dose-response relationship observed[1]

[1]Burris et al, ASH 2014, Abstract # 1984

Trial Design: TGR-1202 + Ublituximab

- Enrolling B-cell NHL and CLL/SLL
- No limit on prior therapies
- Allows for prior BTK and/or PI3K inhibitors use
- 3+3 Dose escalation

Ublituximab		TGR-1202	
CLL: 600mg NHL: 900mg	+	800mg	Completed
CLL: 600mg NHL: 900mg	+	1200mg	Completed
900mg	+	400mg micronized	Completed
900mg	+	600 mg micronized	Completed
900mg	+	800 mg micronized	Enrolling

Dose Escalation Until MTD

Cycle 1 Days 1, 8, 15 | *Cycle 2* Days 1, 8, 15 | *Cycle 4* Day 1 | *Cycle 6* Day 1 | *Cycle 9* Day 1 | *Cycle 12* Day 1 — Ublituximab

TGR-1202 Once Daily Continuously (Days 1-28 = 1 Cycle)

Demographics: TGR-1202 + Ublituximab

Evaluable for Safety (n)		27
Evaluable for Efficacy† (n)		26
Median Age, years (range)		65 (35 – 82)
Male/Female		17/10
ECOG, 0/1/2		12/15/0
Prior Therapies, median (range)		3 (1 – 9)
Histologies	CLL/SLL, n	9/1
	Follicular, n	9
	DLBCL, n	7
	Richter's, n	1
≥ 2 Prior R–Chemo Regimens, n		18 (67%)
Refractory to Prior Therapy, n		11 (41%)

†1 CLL not eligible per failed Inc/Exc

- 67% of CLL had 17p and/or 11q del
- Median Prior Tx in FL: 5 (range 1 – 9)
- 5/7 DLBCL with Germinal Center (GCB) Subtype

Safety: TGR-1202 + Ublituximab

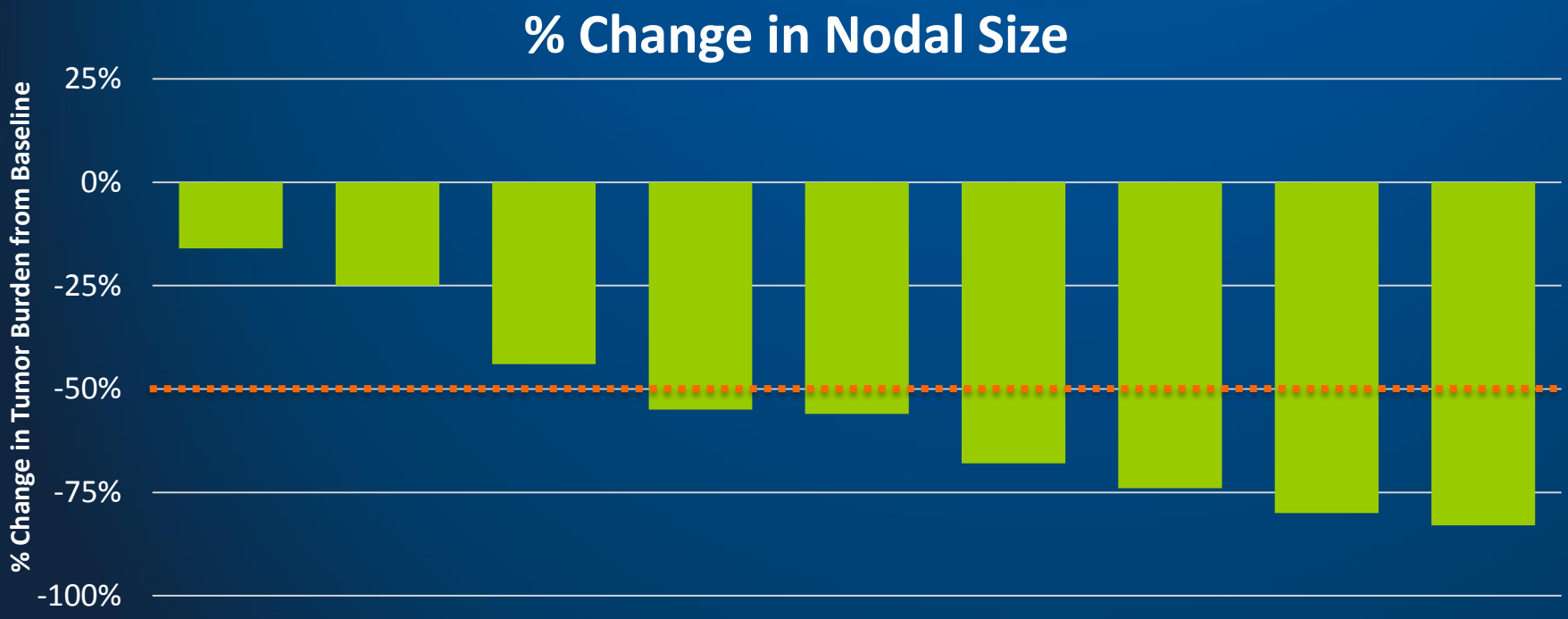
Adverse Events in ≥10% (All Causality) n=27

Adverse Event	All Grades n (%)	Grade 3/4 n (%)
Infusion reaction	14 (52)	1 (4)
Neutropenia	11 (41)	9 (33)
Nausea	10 (37)	-
Diarrhea	9 (33)	-
Fatigue	8 (30)	-
Insomnia	8 (30)	-
Dyspnea	6 (22)	1 (4)
Cough	5 (19)	-
Back Pain	4 (15)	-
Constipation	4 (15)	-
Sinusitis	4 (15)	-
Vomiting	4 (15)	-
Abdominal Pain	3 (11)	1 (4)
Fever	3 (11)	2 (7)
Upper Resp Inf	3 (11)	-

- **IRR mostly on Day 1**
- **3 patients enrolled with Gr 3 neutropenia**
  - 2 improved & 1 worsened (DLT)
  - GCSF restricted in Cycle 1
- **TGR-1202 dose reduced in 1 patient in Cycle 5**
  - Grade 1 diarrhea
- **Notably, no hepatic toxicity observed**

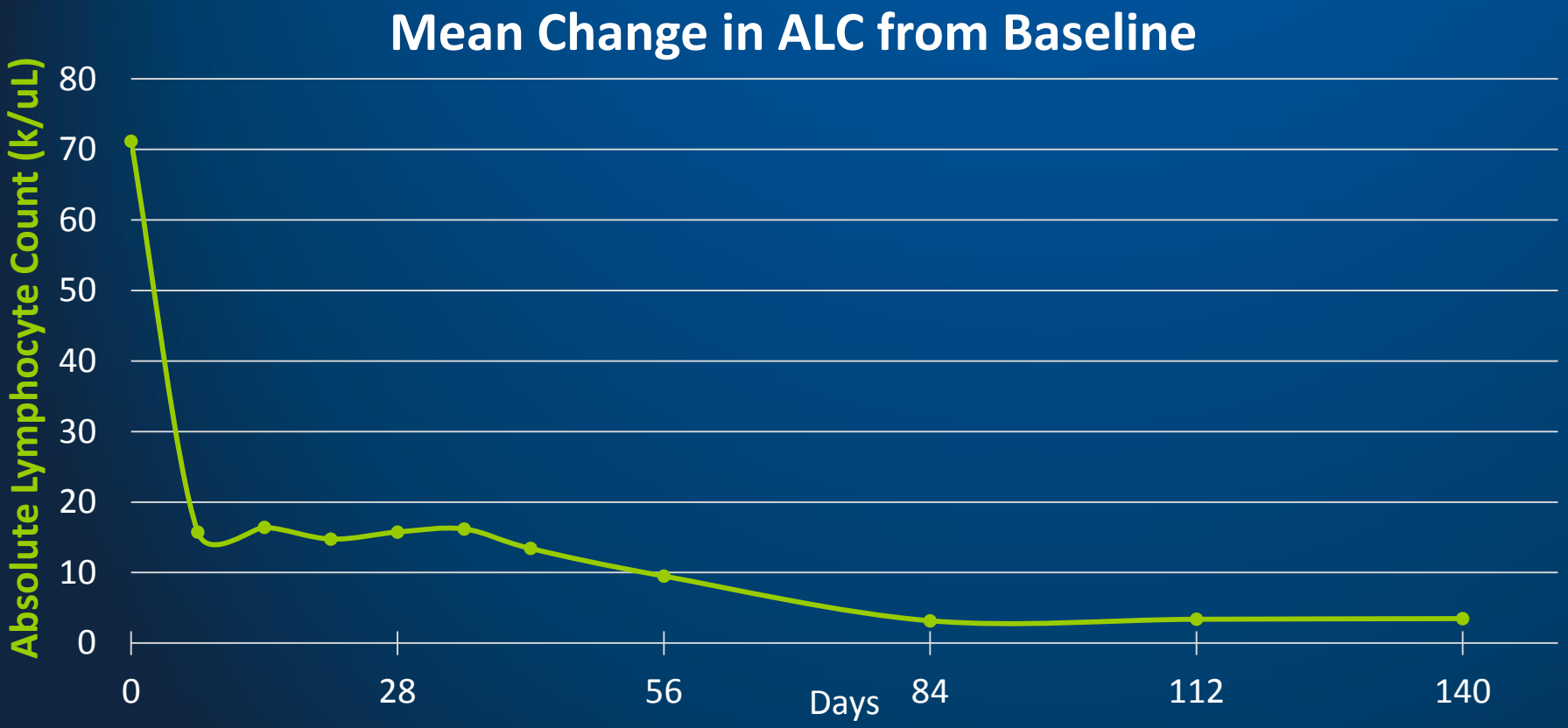
Activity in CLL/SLL: TGR-1202 + Ublituximab

Interim Data From Early Dose Escalation Cohorts



- 67% PR rate iwCLL (Hallek 2008)
- 6/9 patients with 17p and/or 11q
- All CLL patients remain on study (3+ to 9+ months)

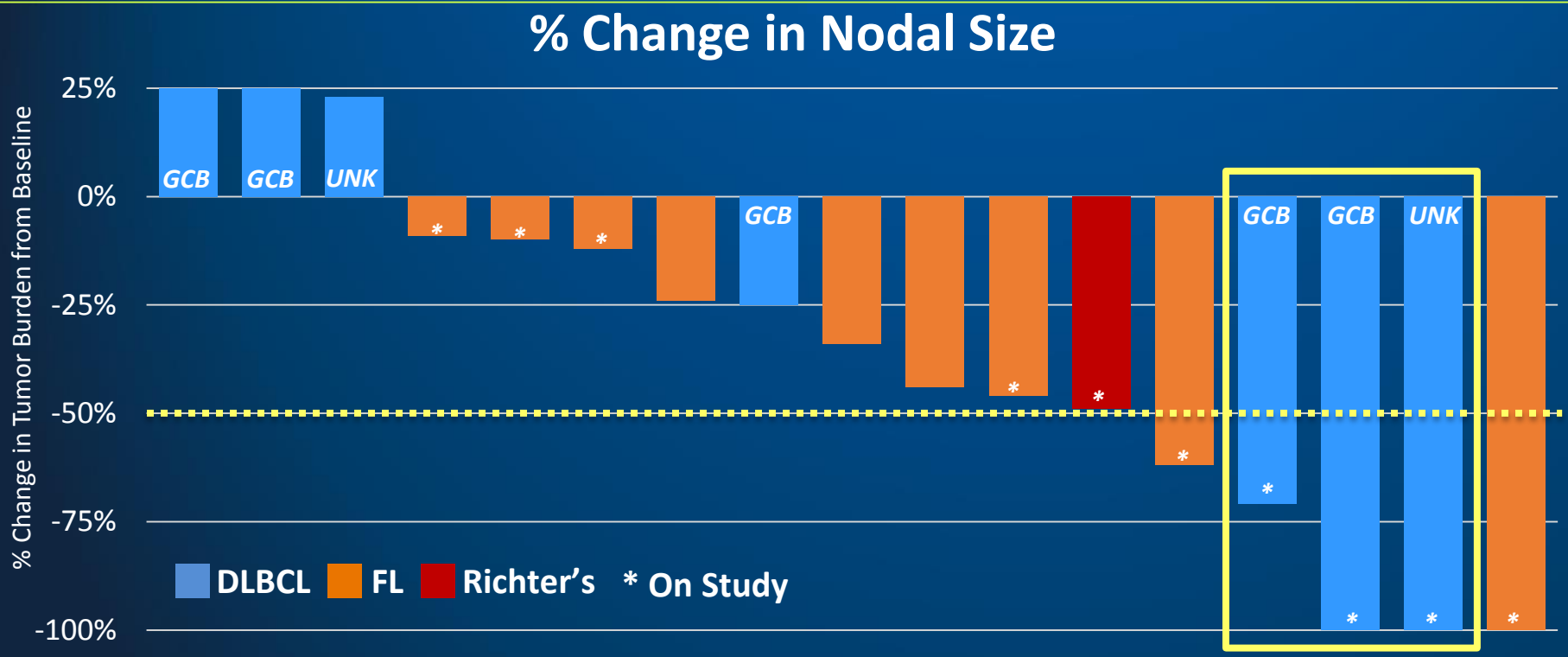
TGR-1202 + Ublituximab: Activity in CLL



- **End of Cycle 3:**
  - **All patients achieved >50% reduction of ALC**
  - **88% achieved ALC <5000/uL**

Activity in NHL: TGR-1202 + Ublituximab

Interim Data From Early Dose Escalation Cohorts



- FL: 1 PET(-) CR and 1 PR
  - 78% of FL (N=9) patients have not progressed on study
- DLBCL: ORR 43% (3/7);
  - 2 CR's confirmed by independent radiologic review
  - 3 patients remain on study > 7 months

"Triplet": TGR-1202 + Ublituximab + Ibrutinib

- **Initial cohorts for both NHL and CLL (n=5)**

Ublituximab		TGR-1202		Ibrutinib
900mg	+	400 mg micronized	+/-	CLL: 420mg NHL: 560mg

  - Ongoing enrollment with 600 mg dose of TGR-1202 in NHL cohort
- **Safety: All Grade 1/2 AEs (no Grade 3/4 events to date)**
  - AEs included IRR, nausea, fatigue, and diarrhea
  - No dose reductions or delays with patients treated up to 4+ months

Clinical Response at First Assessment (8 Weeks)

Histology	Description	Prior # Rx	Prior Ibrutinib	Rel/Ref	Rituximab Refractory	Response	% ↓
Follicular	Stage IV	4	Refractory	Refractory	Yes	PR	74%
MCL	Advanced	2	No	rAuto txp	No	CR	PET -
Richter's	17p	3	No	Refractory	Yes	PD	N/A
CLL	17p	2	No	Refractory	Yes	Too Early	N/A
Follicular	Stage IV	1	No	Refractory	Refractory	Too Early	N/A

Conclusions

- **Ublituximab and TGR-1202 has significant activity:**
  - **CLL:** ORR 67% iwCLL (Hallek 2008)
  - **FL:** 78% have not progressed on study
  - **DLBCL:** ORR 43%, with 2 confirmed CRs (activity in GCB)
- **Favorable toxicity profile**
  - No hepatic toxicity to date in 87 pts
    - 32 pts in current study + 55 pts in single agent TGR-1202 Ph 1
- **Both the "Doublet" and "Triplet" continue to accrue**
  - Clinicaltrials.gov: NCT02006485

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