UBLITUXIMAB (TG-1101), A NOVEL GLYCOENGINEERED ANTI-CD20 MAB, IN COMBINATION WITH IBRUTINIB ACHIEVES 95% ORR IN PATIENTS WITH HIGH-RISK RELAPSED/REFRACTORY CLL

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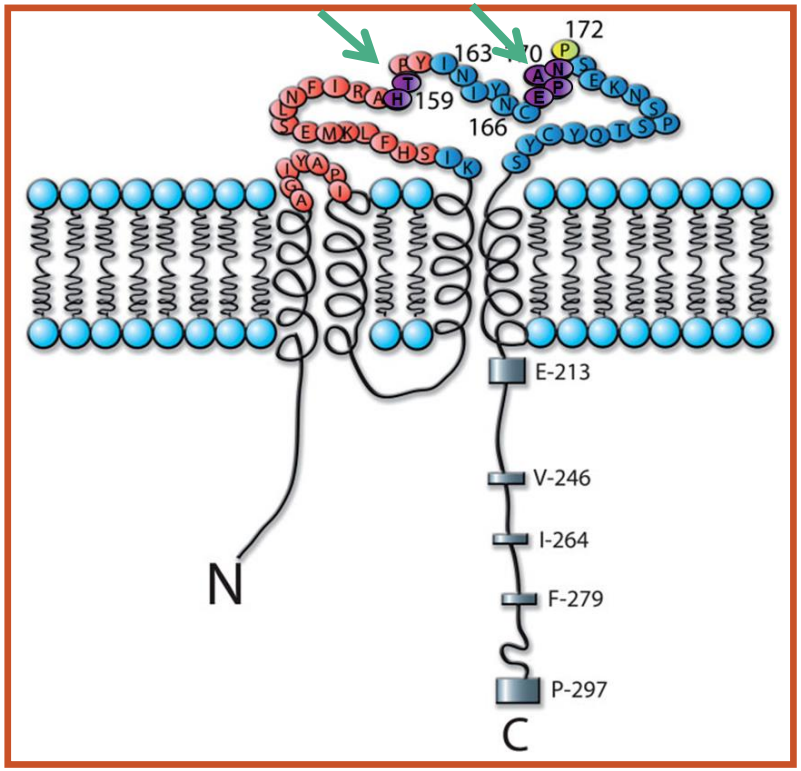
Ublituximab: Glycoengineered Anti-CD20 mAb

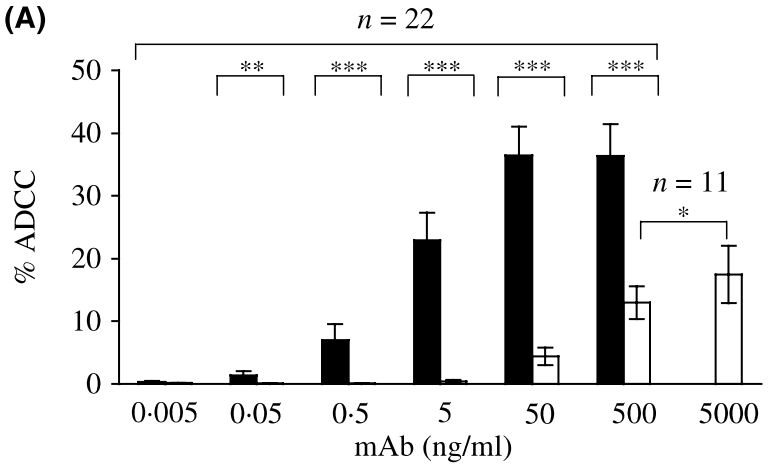
- Type 1 chimeric IgG1 mAb
- Unique binding sequence on CD20 (**Green** arrows in figure)
- Glycoengineered to contain low fucose content
- Activity in “low” CD20 expressing cell lines

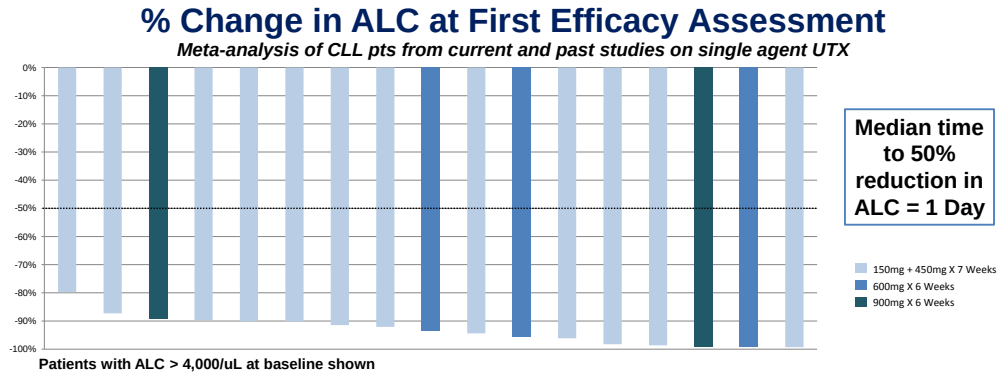


O’Connor et al, ASCO 2014

Figure Adapted from Ruuls et al 2008

Properties of ublituximab in preclinical and phase I studies

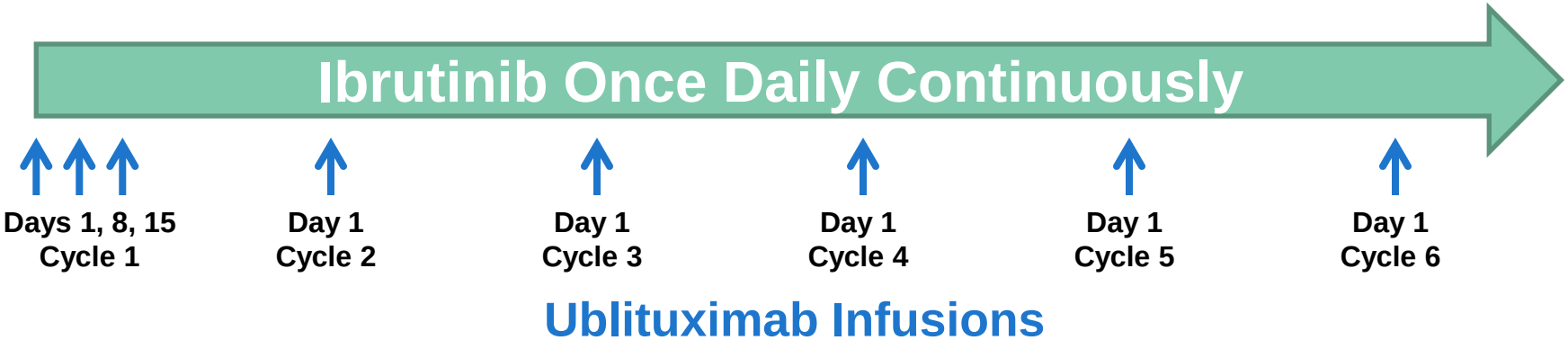




- Leads to higher NK cell-mediated ADCC than rituximab (black vs. white bars)
- Has significant single-agent activity in CLL and other B-cell malignancies, including rituximab-refractory

De Romeuf C et al. Brit J Haematol 2008. 140:635.
O'Connor O et al. ASCO 2014, abstract 8524.

Study Design: Ublituximab + Ibrutinib



Dose Escalation Schema:

Cohort	Ublituximab	Ibrutinib
1	600 mg	420 mg
2	900 mg	420 mg

- Two part study to determine the safety and efficacy of ublituximab in combination with ibrutinib
  - Part 1: 6 patient per cohort safety run-in
  - Part 2: Open enrollment at fixed dose
- After cycle 6, all patients off study and may remain on single agent ibrutinib per investigator discretion

Endpoints

- Part 1 (safety run-in)
  - Primary: safety
- Part 2 (expansion)
  - Primary: ORR
  - Secondary: safety, CR rate, MRD negativity in CLL
- Responses in CLL determined by IWCLL 2008

Eligibility Criteria

- Relapsed CLL, small lymphocytic lymphoma, mantle cell lymphoma
- Preliminary overall results presented as poster at ASH 2014[1]
- CLL eligibility criteria
  - Age at least 18 years
  - At least 1 prior regimen
  - Indication for therapy
  - Cytogenetic and/or FISH available (determined locally)
  - ECOG ≤ 2
  - Bilirubin ≤ 1.5 x ULN, AST ≤ 2.5-5 x ULN
  - Creatinine ≤ 2 mg/dL or clearance ≤ 50 mL/min
  - ANC > 1,000/µL and platelets > 50k/µL for Part 1; and
  - ANC > 750/µL and platelets > 30k/µL for Part 2
  - Prior treatment with a BTK inhibitor and/or a PI3K inhibitor permitted
  - Patients with Richter's transformation excluded

[1]Sharman J et al. ASH 2014, abstract 4679.

Patient Characteristics

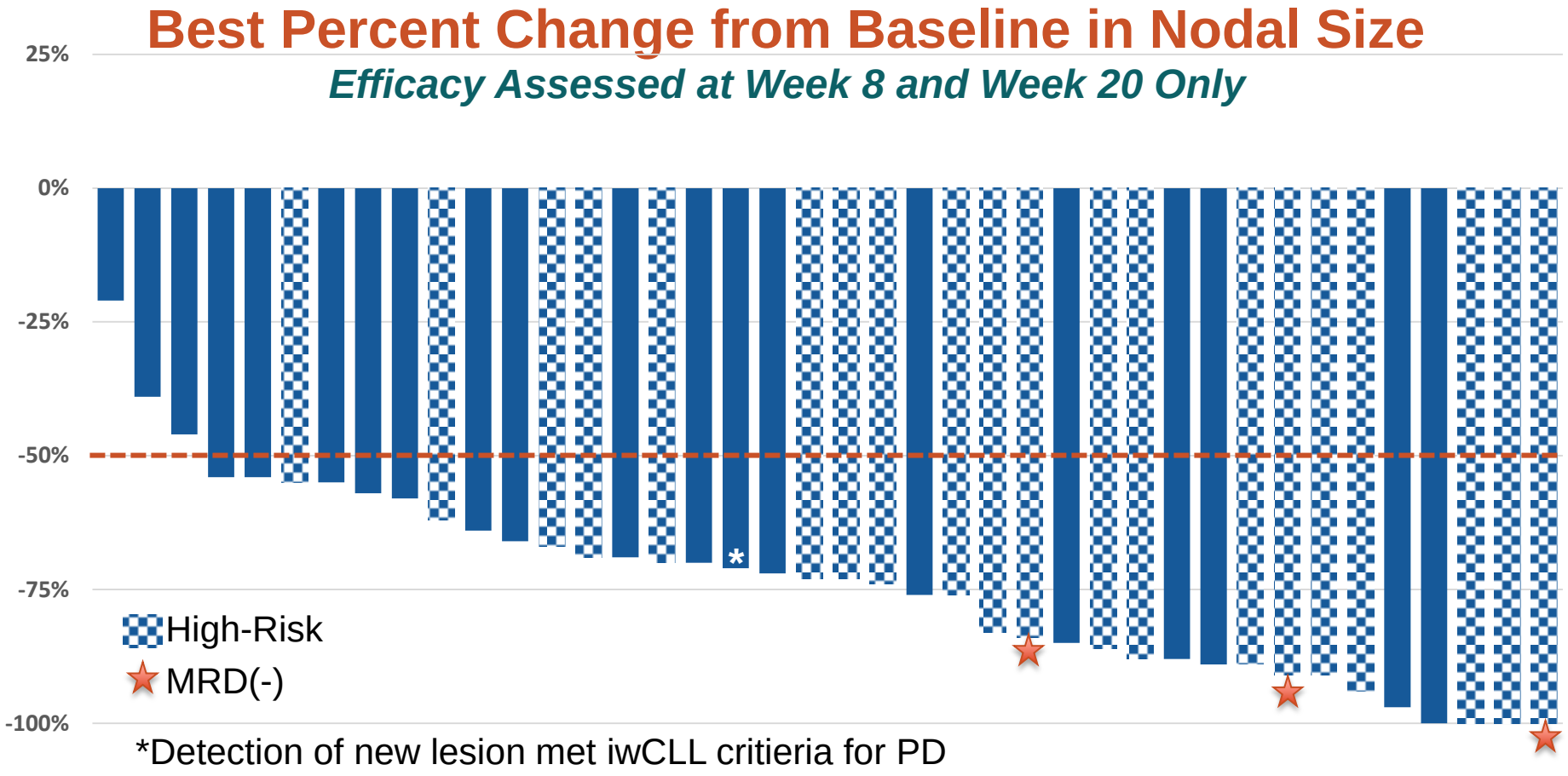
Evaluable for Safety, (n)	44
Evaluable for Efficacy, † (n)	40
Median Age, years (range)	71 (39 – 86)
Male/Female	22/22
ECOG, median	1
Prior Regimens, median (range)	2 (1 – 7)
≥ 3 Prior Regimens	16 (36%)
Prior Anti-CD20 (rituximab, ofatumumab, obintuzumab)	41 (93%)
Refractory to anti-CD20	13 (33%)
Prior Alkylating Agent	28 (64%)
Prior Purine Analog	22 (50%)
High-risk (17p del, 11q del, p53 mutated)	21 (48%)

†4 patients not evaluable: 2 patients withdrew consent and 2 patients came off study prior to first disease assessment: 1 due to ibrutinib related AE (diarrhea); 1 due to multiple non-drug related AE's

Safety

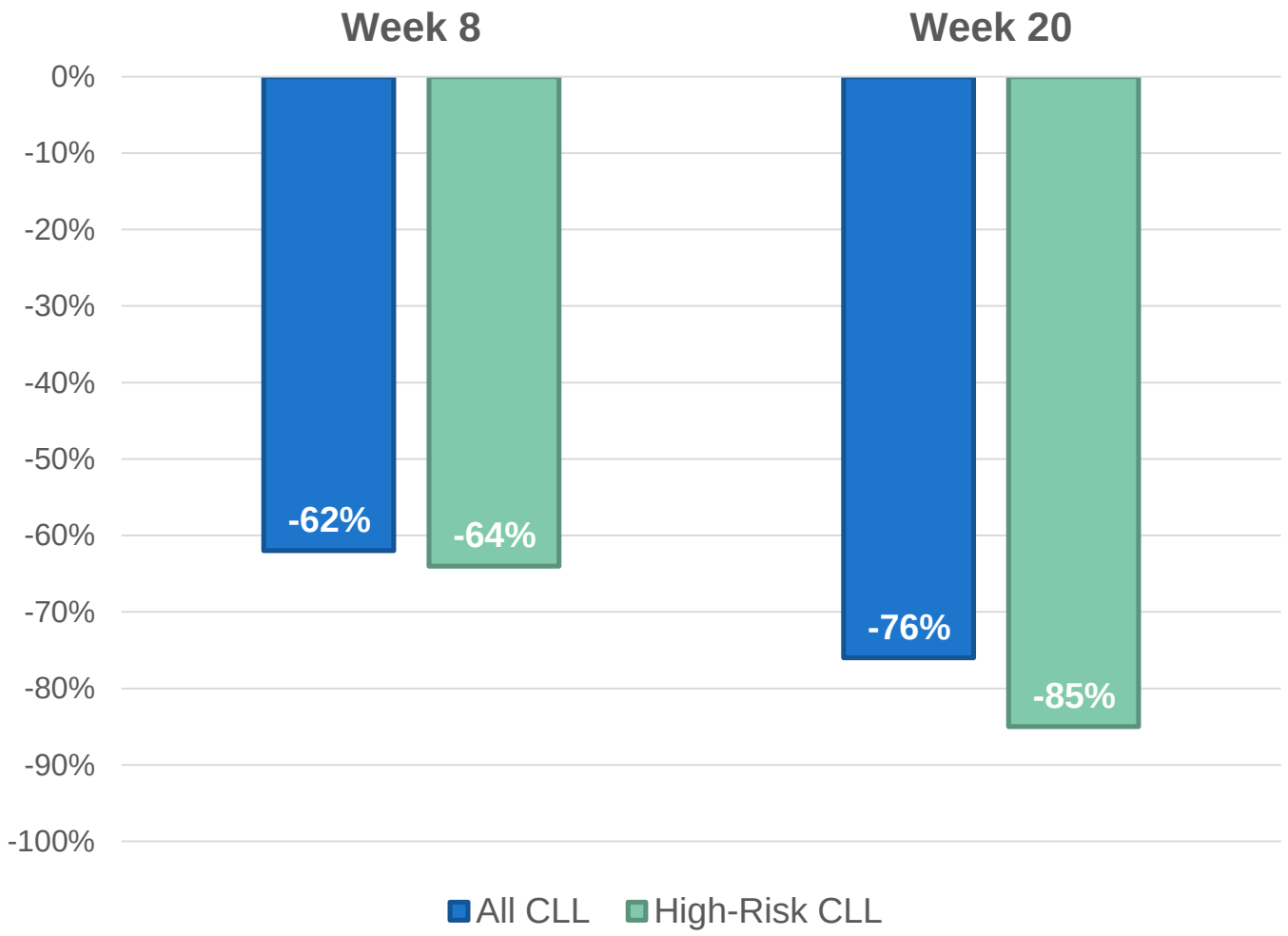
All Causality AE's in > 10% of Patients (n=44)		
Adverse Event	**All Grades** n (%)	**Grade 3/4** n (%)
Infusion reaction	20 (45%)	3 (7%)
Diarrhea	16 (36%)	2 (5%)
Fatigue	13 (30%)	1 (2%)
Nausea	11 (25%)	-
Rash	10 (23%)	-
Pyrexia	8 (18%)	-
Arthralgia	7 (16%)	1 (2%)
Constipation	7 (16%)	-
Cough	7 (16%)	-
Muscle Spasms	7 (16%)	-
Peripheral Edema	7 (16%)	-
Upper Respiratory Tract Infection	7 (16%)	-
Dizziness	6 (14%)	-
Anemia	5 (11%)	5 (11%)
Contusion	5 (11%)	-
Headache	5 (11%)	-
Myalgia	5 (11%)	-
Neutropenia	5 (11%)	5 (11%)
Thrombocytopenia	5 (11%)	2 (5%)

Efficacy: Nodal Reductions



- 37/40 (93%) achieved > 50% reduction in nodal size

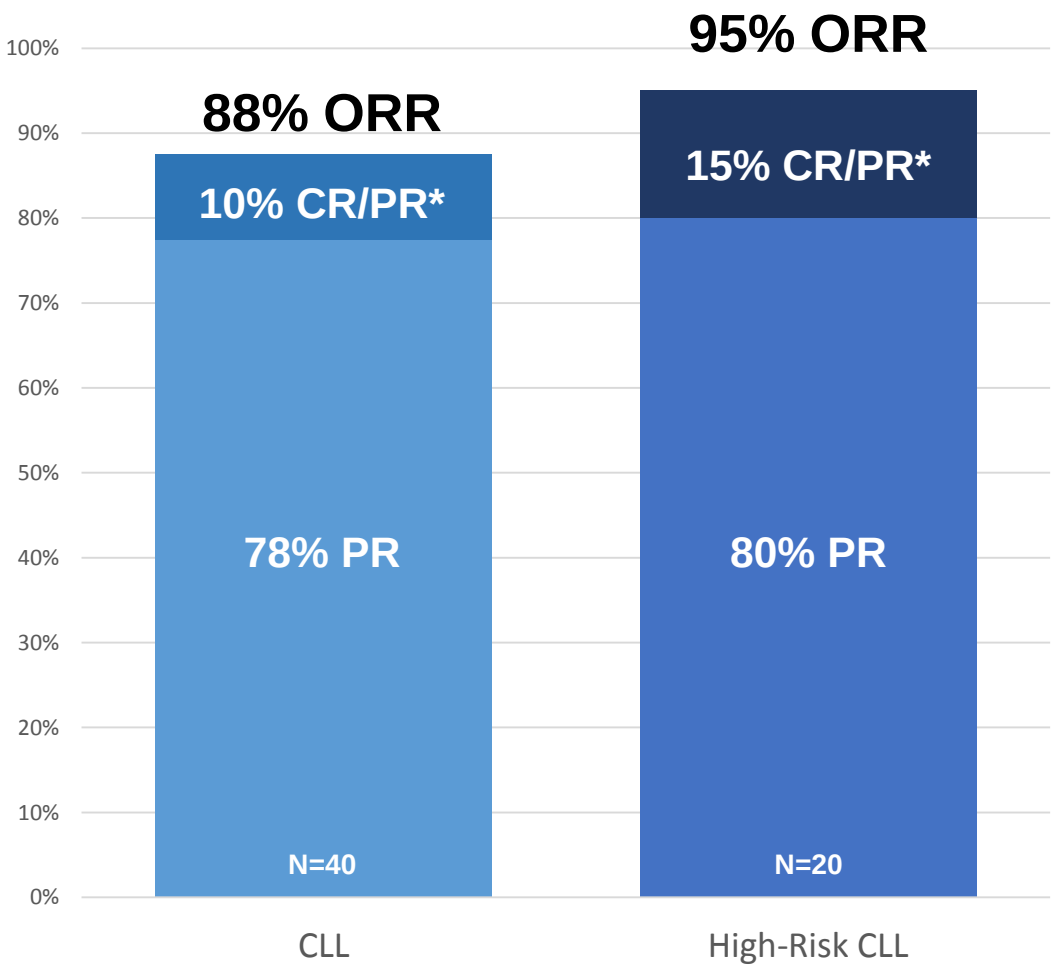
Efficacy: First vs. Second Scan



- “High-Risk” = 17p del, 11q del, or p53 mutation

Efficacy: Best Overall Response Rate

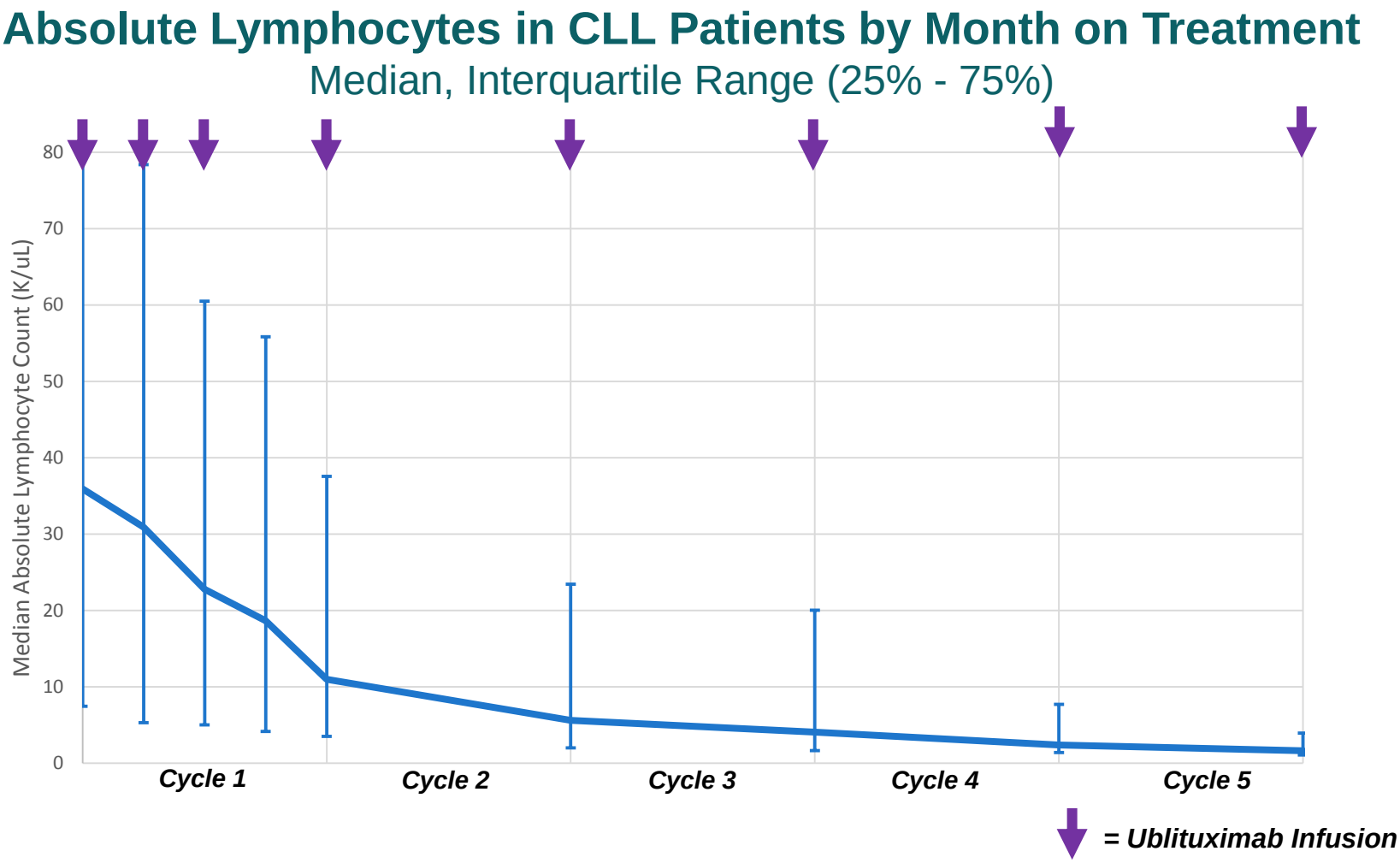
Per study design, all patients were evaluated for efficacy at Month 2 and 5 only



15% of High Risk patients were <u>MRD negative</u> within 6 months of therapy

**2 patients had CR per iwCLL criteria without bone marrow confirmation*

Efficacy: Lymphocytosis

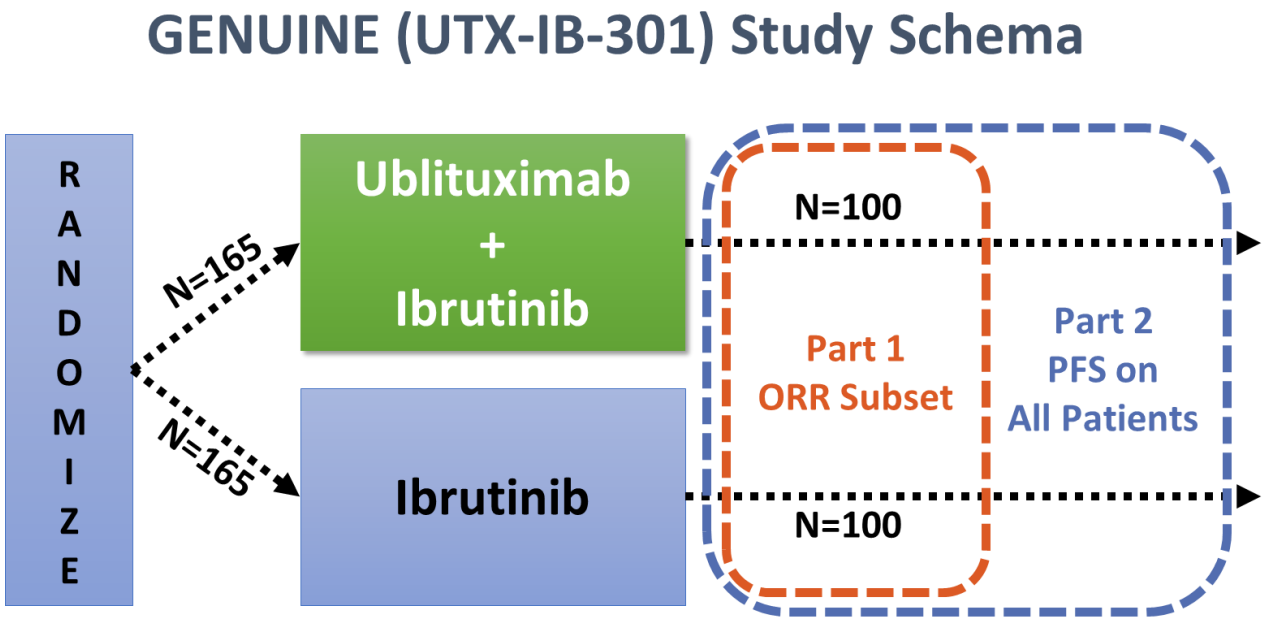


- Median 75% decrease in ALC from baseline by the end of Cycle 3
- 70% of CLL patients had ALC in normal range (<4000/uL) within 6 cycles of therapy

Conclusions

- Addition of ublituximab to ibrutinib in relapsed CLL is safe and effective.
  - Adverse events were as expected and not usually serious
  - Overall response rate 88%, 95% in high-risk
  - Complete response rate 10%, and 3 patients achieved MRD-negative status
  - Mitigates the transient lymphocytosis seen with ibrutinib alone
  - Whether the combination leads to improved clinical outcomes compared with ibrutinib alone is unknown
- Future directions
  - Phase 3 trial of ibrutinib +/- ublituximab in relapsed, high-risk CLL is underway
  - Additional combinations being studied – e.g. ublituximab + ibrutinib + PI3 kinase inhibitor (TGR-1202)

The "GENUINE" Phase 3 Trial: High-Risk CLL



- Design, Endpoints, and Statistics agreed to via Special Protocol Assessment (SPA) with U.S. FDA
- Enrolling 330 patients with High-Risk CLL
  - Presence of 17p del, 11q del, and/or p53 mutation
- Study Chair: Jeff Sharman, MD