Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: results of the GENUINE phase 3 study

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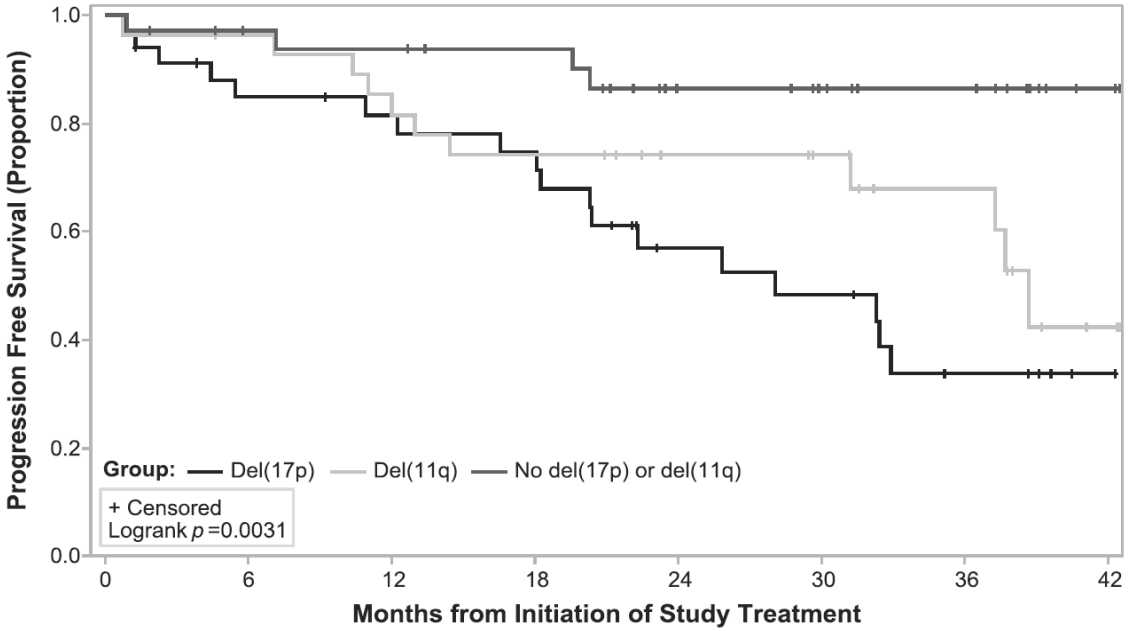
Introduction

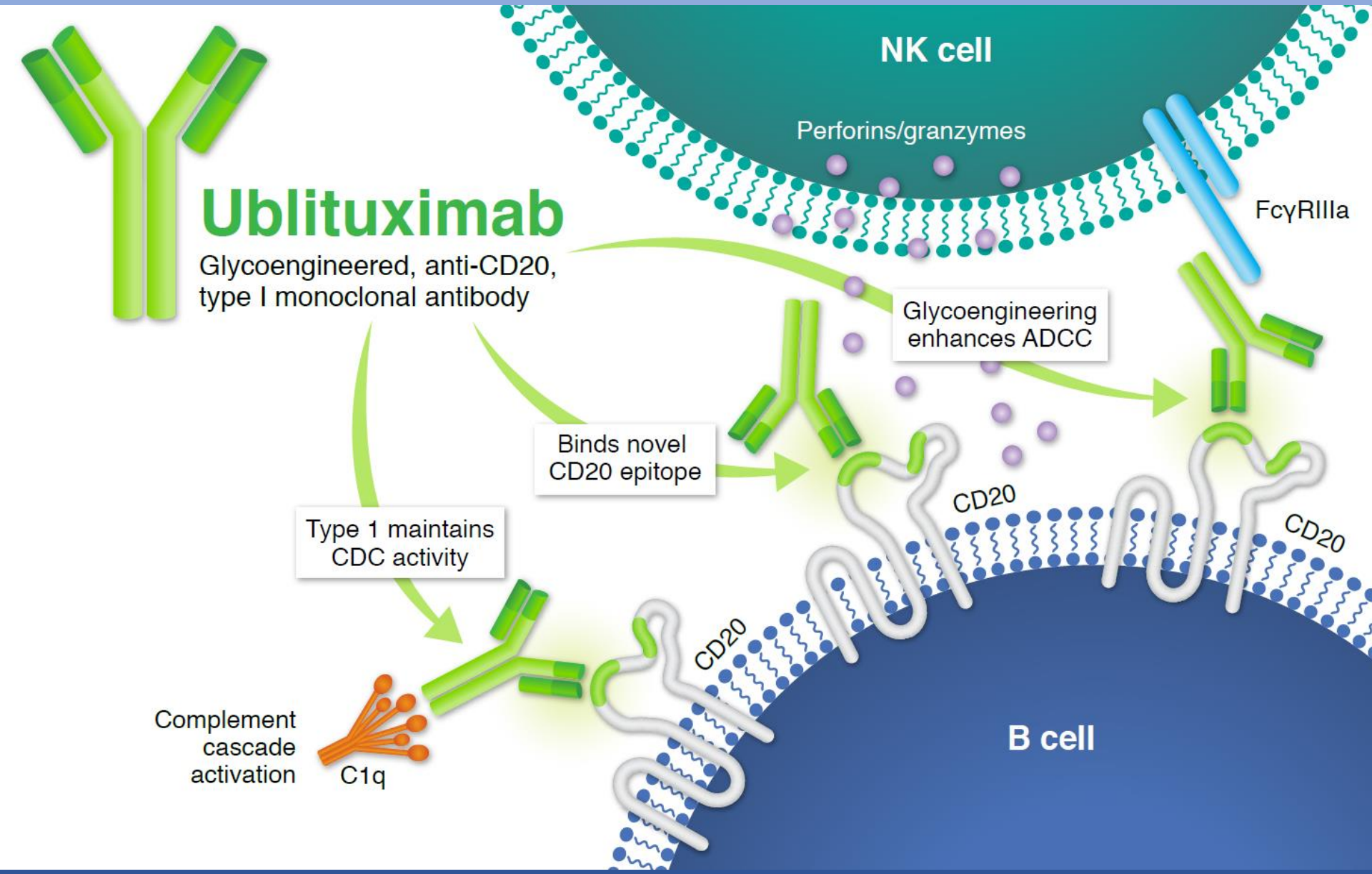
- Ibrutinib represents a paradigm shift in management of CLL demonstrating high rates of durable responses in the front line and relapse settings
- Patients with high risk cytogenetic features have the inferior outcomes on ibrutinib monotherapy
- Improving outcomes for high risk patients treated with ibrutinib remains an unmet medical need



Del(17p) is an independent predictor of inferior CLL progression in a multivariable model: HR 2.14 (1.5-3.96) p=.016

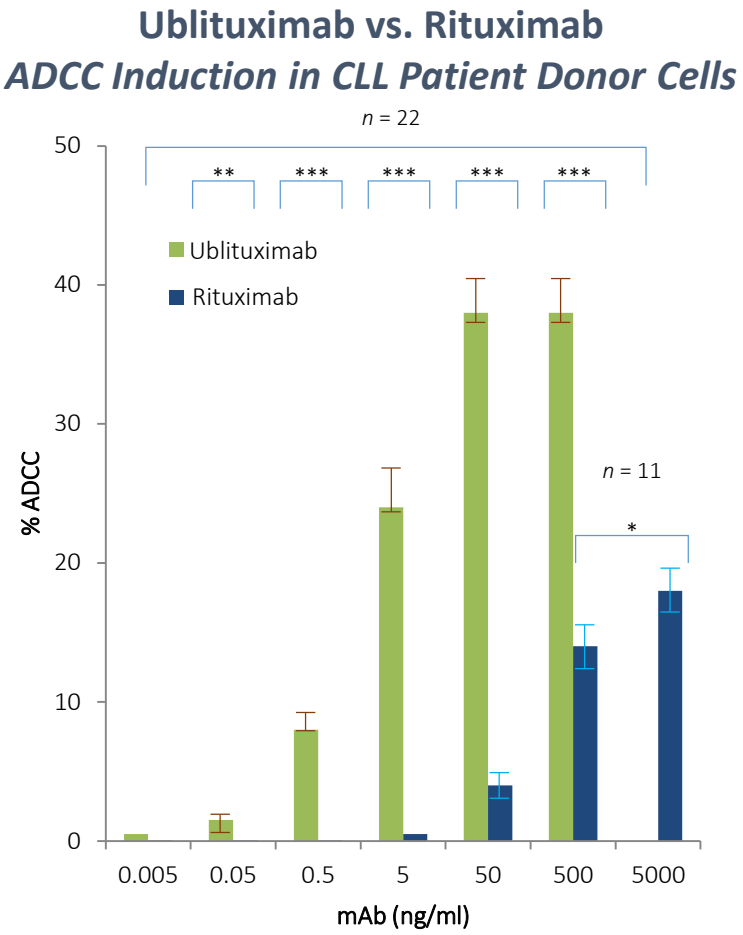
Woyach et al, JCO 2016, Byrd et al, Blood 2015

Ublituximab (TGTX-1101)



Ublituximab (TGTX-1101)

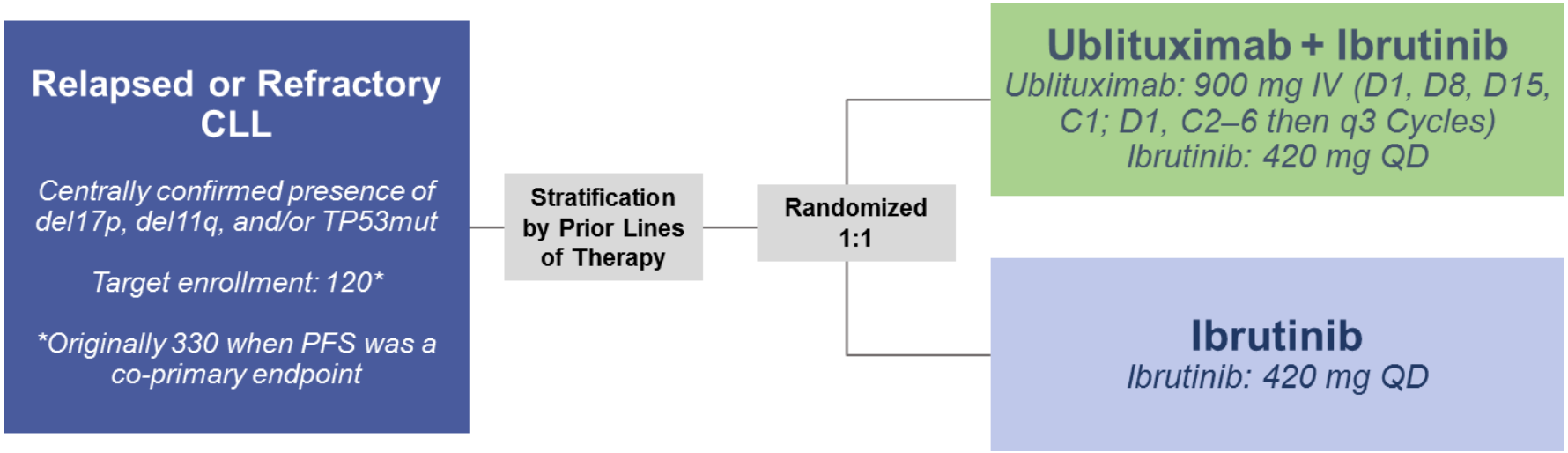
- Ublituximab is more efficient than rituximab in inducing ADCC in preclinical models[1]
- Single agent activity observed in rituximab-refractory patients[2]
- Phase 2 study of ublituximab + ibrutinib in relapsed/refractory CLL:
  - 88% ORR (iwCLL 2008 criteria, investigator assessed)[3]
- 90 minute infusion times[2, 3]



De Romeuf et al, BJH 2008[1]; O'Connor et al, BJH 2016[2]; Sharman et al, BJH 2016[3]

UTX-IB-301 (GENUINE) Study Design

- Open-label, multicenter, randomized, Phase III study in relapsed or refractory high-risk CLL (del17p, del11q, or TP53 mutated)
- Originally designed with ORR and PFS as co-primary endpoints
  - Due to enrollment challenges, target enrollment was lowered and removed PFS as a co-primary



- Response assessments occurred at Week 8, 16, and 24, and every 12 weeks thereafter

Study Endpoints

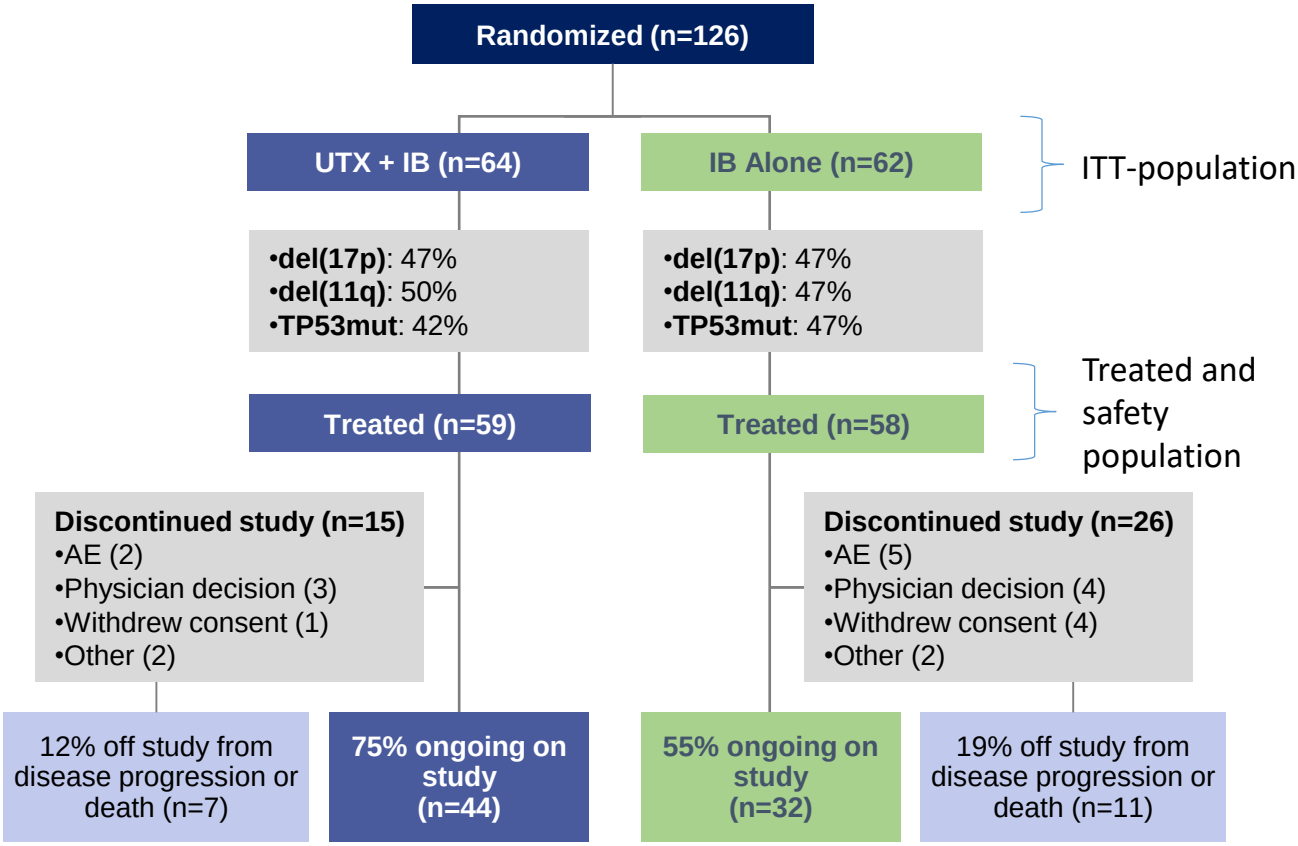
- **Primary endpoint:** Overall Response Rate as assessed by Independent Central Review Committee (IRC) by iwCLL (Hallek 2008) criteria
  - Evaluated when all enrolled patients had at least two efficacy evaluations
- **Secondary endpoints:**
  - CR rate
  - MRD negativity (peripheral blood; 7-color flow)
  - PFS, DOR, TTR
  - Safety profile
- **Statistical Assumptions:**
  - 120 patients required to have 90% power to detect an absolute difference in ORR of approximately 30%

Key Eligibility Criteria

- Age ≥18 yr
- Relapsed/refractory CLL requiring treatment
  - Utilizing FISH and NGS, centrally confirmed presence of **del(17p), del(11q), and/or TP53 mutation**
- Measurable disease
- ECOG ≤2
- No history of transformation of CLL
- No prior BTK inhibitor therapy

Patient Disposition

- 126 patients randomized, 9 never treated
- 100% were genetically high risk per protocol
- 64% of UTX + IB patients and 66% of IB Alone patients were del(17p) or TP53 mutated
- 36% of UTX + IB patients and 34% of IB Alone patients were del(11q) only
- Median follow up: 11.4 months



Data Cutoff: February 15, 2017

Demographics

	Ublituximab + Ibrutinib n=64	Ibrutinib n=62
Mean age, years (range)	67 (43 - 87)	67 (51-86)
Mean time from diagnosis to randomization, years (range)	6.6 (3 mos – 22 yrs)	6.5 (3 mos – 20 yrs)
Male	44 (69%)	46 (74%)
ECOG performance status at baseline		
0–1	61	60
2	3	2
Rai stage III-IV, %	32 (50%)	26 (42%)
IGHV unmutated, %	51 (80%)	51 (82%)
Bulky disease at baseline (≥ 5cm)	29 (45%)	16 (26%)
Number of prior lines of therapy, median (range)	3 (1-7)	3 (1-8)
Most common prior regimens		
FC ± Rituximab	30 (47%)	29 (47%)
BR	27 (42%)	29 (47%)
Rituximab	54 (84%)	57 (92%)
Obinutuzumab ± Chlorambucil	5 (8%)	4 (6%)
Idelalisib ± Rituximab	5 (8%)	4 (6%)

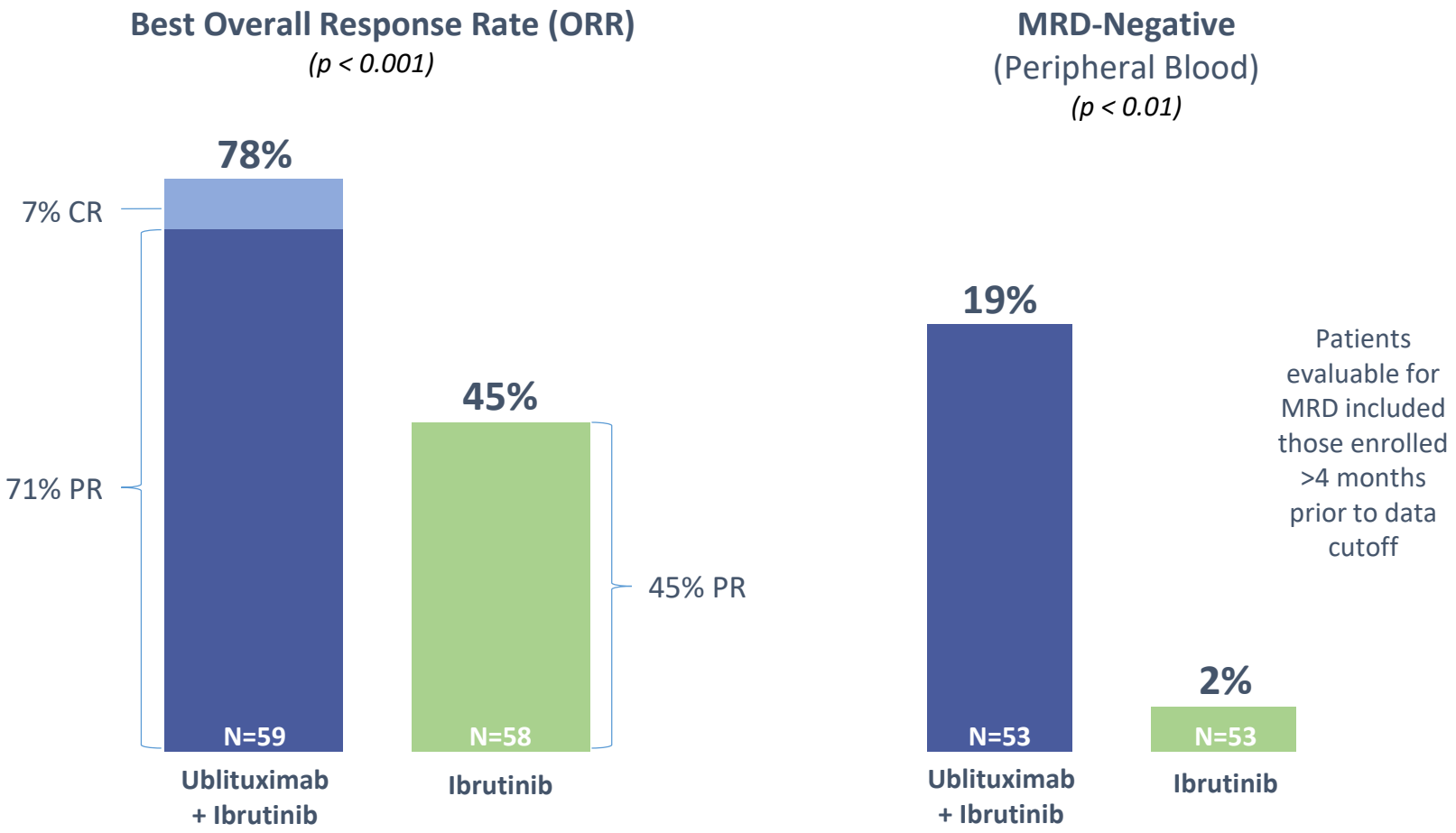
Safety: Adverse Event Summary (≥ 10%)

	Ublituximab + Ibrutinib (N=59)		Ibrutinib (N=58)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Infusion reaction	54%	5%	-	-
Diarrhea	42%	3%	40%	3%
Fatigue	27%	-	33%	2%
Insomnia	24%	-	10%	2%
Nausea	22%	-	21%	2%
Headache	20%	-	28%	2%
Arthralgia	19%	2%	17%	-
Cough	19%	-	24%	-
Abdominal Pain	15%	-	9%	-
Stomatitis	15%	2%	9%	2%
Upper Respiratory Infection	15%	-	12%	2%
Dizziness	15%	-	22%	2%
Contusion	15%	-	29%	-
Anemia	14%	5%	17%	7%
Peripheral Edema	10%	-	21%	-
Adverse Events <10% of Special Interest				
Pneumonia	5%	0%	9%	5%
Atrial Fibrillation	3%	3%	5%	2%
Febrile Neutropenia	3%	3%	2%	2%

Safety: Key Laboratory Abnormalities

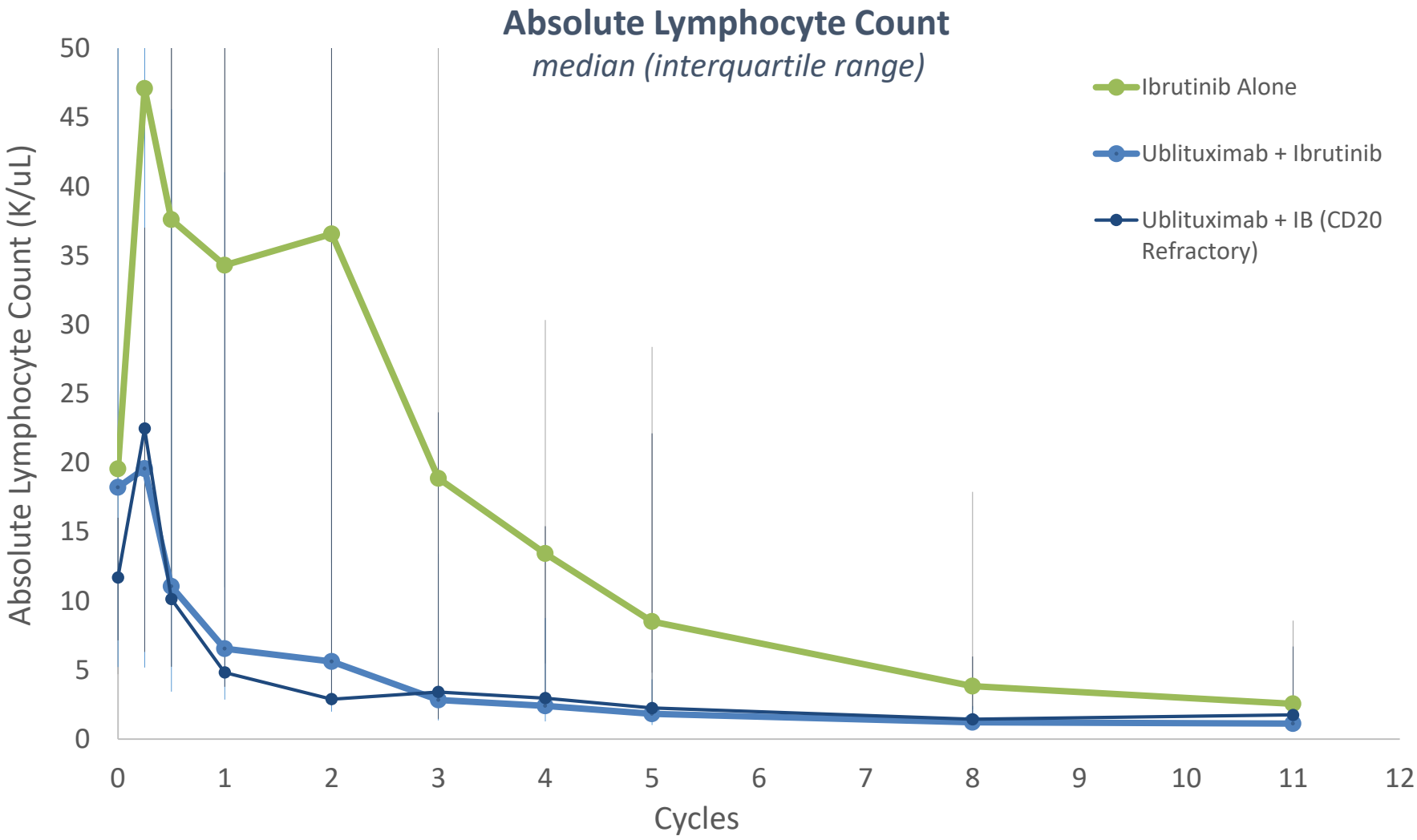
	Ublituximab + Ibrutinib (N=59)		Ibrutinib (N=58)	
	Any Grade n (%)	**Grade ≥3** n (%)	**Any Grade** n (%)	**Grade ≥3** n (%)
ALT elevation	1 (2%)	-	2 (3%)	1 (2%)
AST elevation	1 (2%)	-	2 (3%)	1 (2%)
Anemia	8 (14%)	3 (5%)	10 (17%)	4 (7%)
Neutropenia	13 (22%)	5 (9%)	7 (12%)	6 (10%)
Thrombocytopenia	8 (14%)	-	6 (10%)	2 (3%)
Blood creatinine increase	5 (9%)	-	1 (2%)	-
Blood uric acid increase	5 (9%)	-	1 (2%)	-

Efficacy: IRC Assessed ORR, CR, & MRD-Negativity



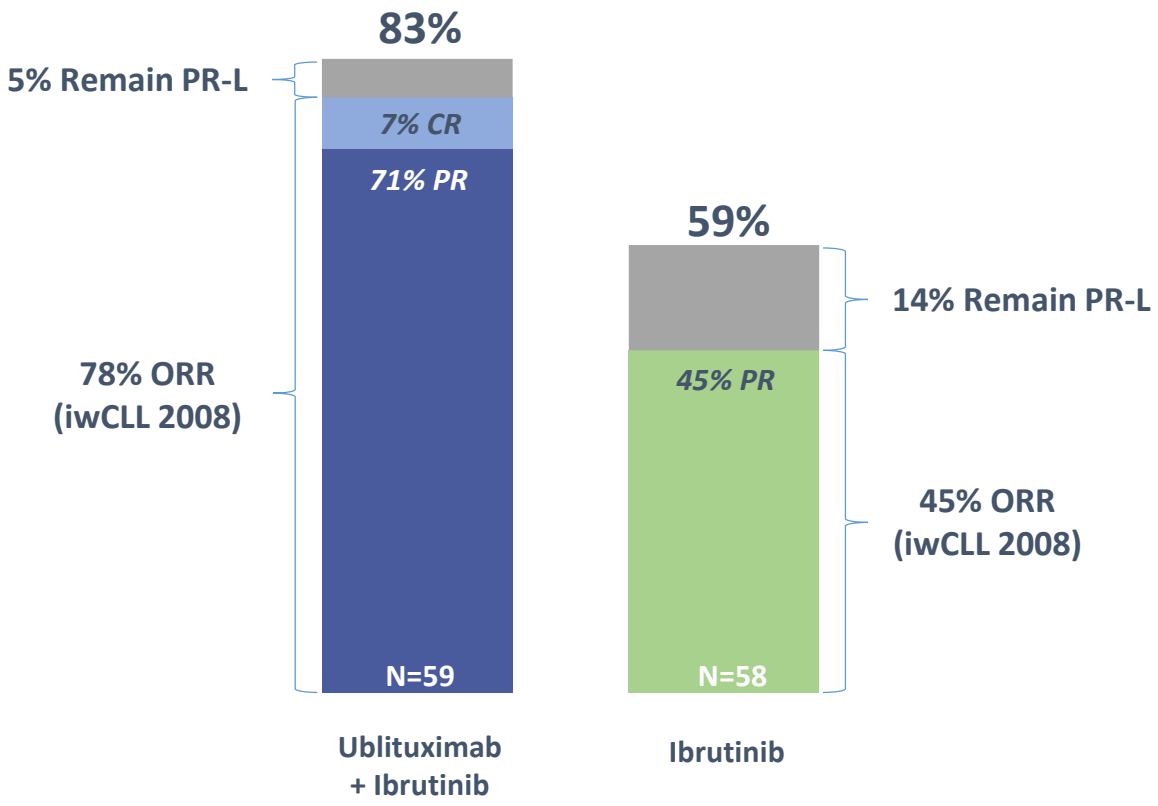
ITT ORR: p < 0.01

Lymphocytosis

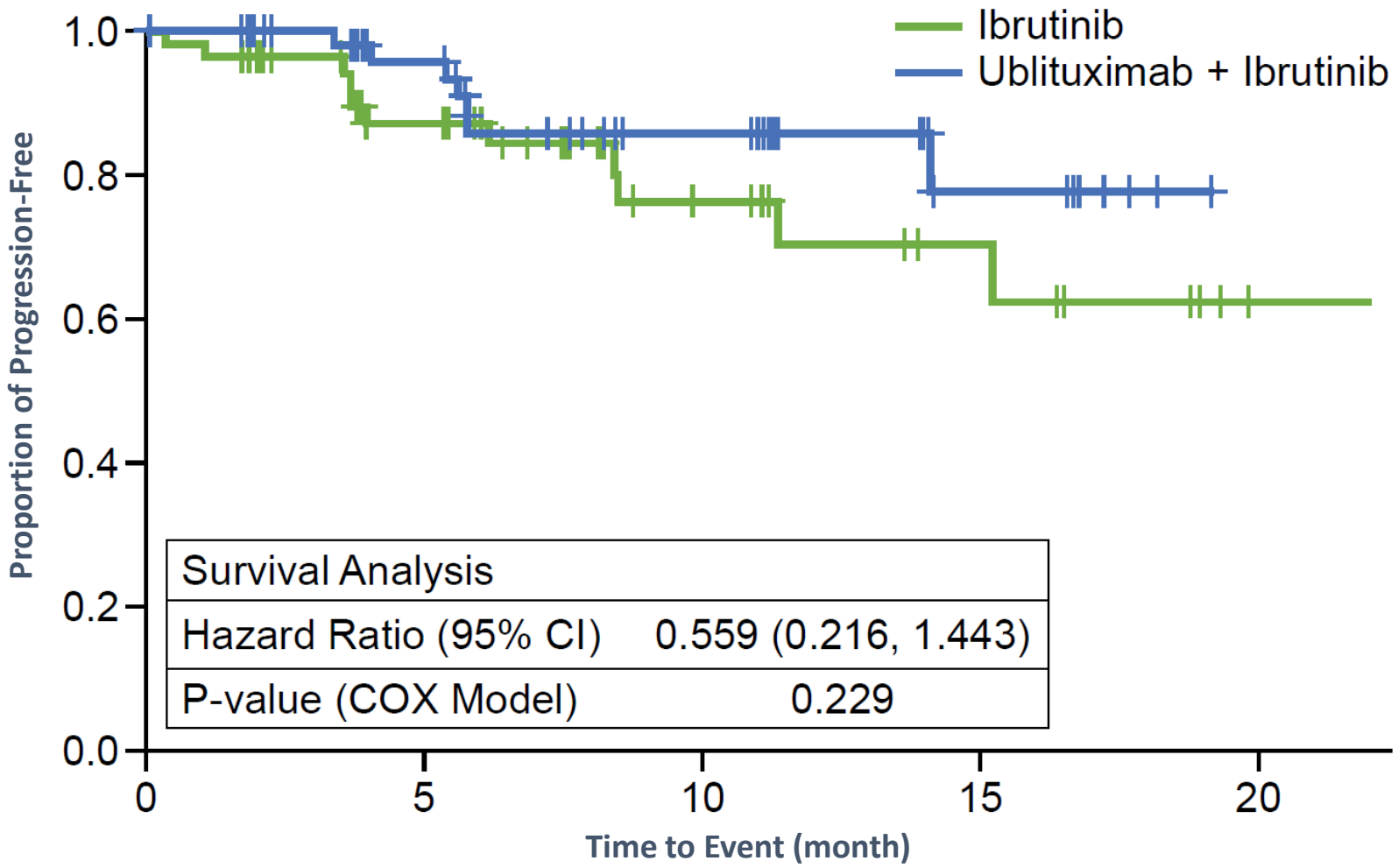


Efficacy: Impact of including "PR-L" on ORR

Best "Possible" Overall Response Rate (ORR)
Including Active PR-L patients
($p < 0.01$)



Efficacy: IRC-Assessed PFS



Ubli + IB	59 (0)	41 (2)	25 (6)	9 (7)	0 (7)
IB Alone	58 (0)	35 (6)	16 (9)	8 (11)	1 (11)

Conclusions

- The GENUINE study met its primary endpoint, demonstrating that the combination of **ublituximab and ibrutinib** yields superior ORR to ibrutinib alone in high-risk CLL
  - ORR 78% (UTX+IB) vs. 45% (IB), $p<0.001$
  - CR rate 7% vs. 0% (secondary endpoint)
  - MRD- rate 19% vs 2% (secondary endpoint), $p<0.01$

- We observed a trend (HR=0.559) in improvement of PFS however not statistically significant at time of analysis

- With the exception of IRRs and grade ≤ 2 neutropenia, ublituximab did not alter the safety profile of ibrutinib monotherapy

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