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

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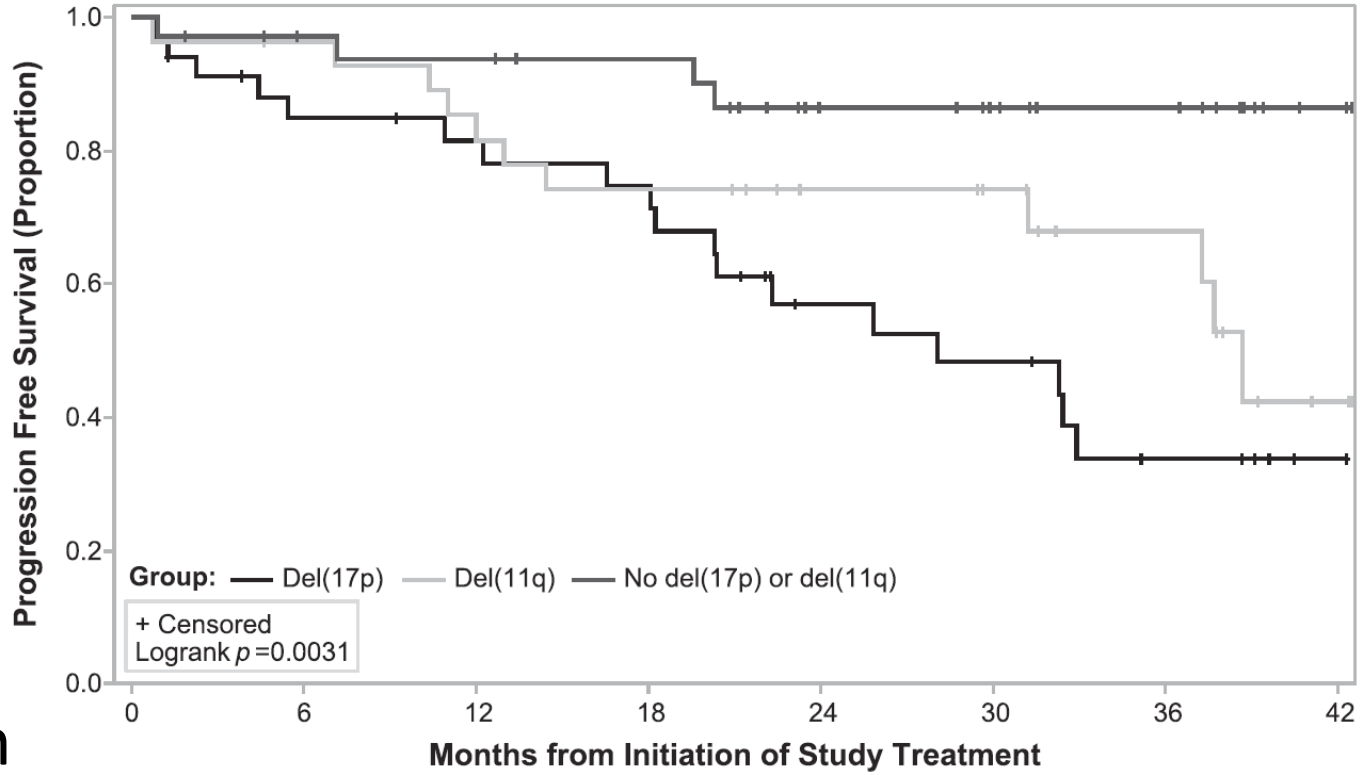
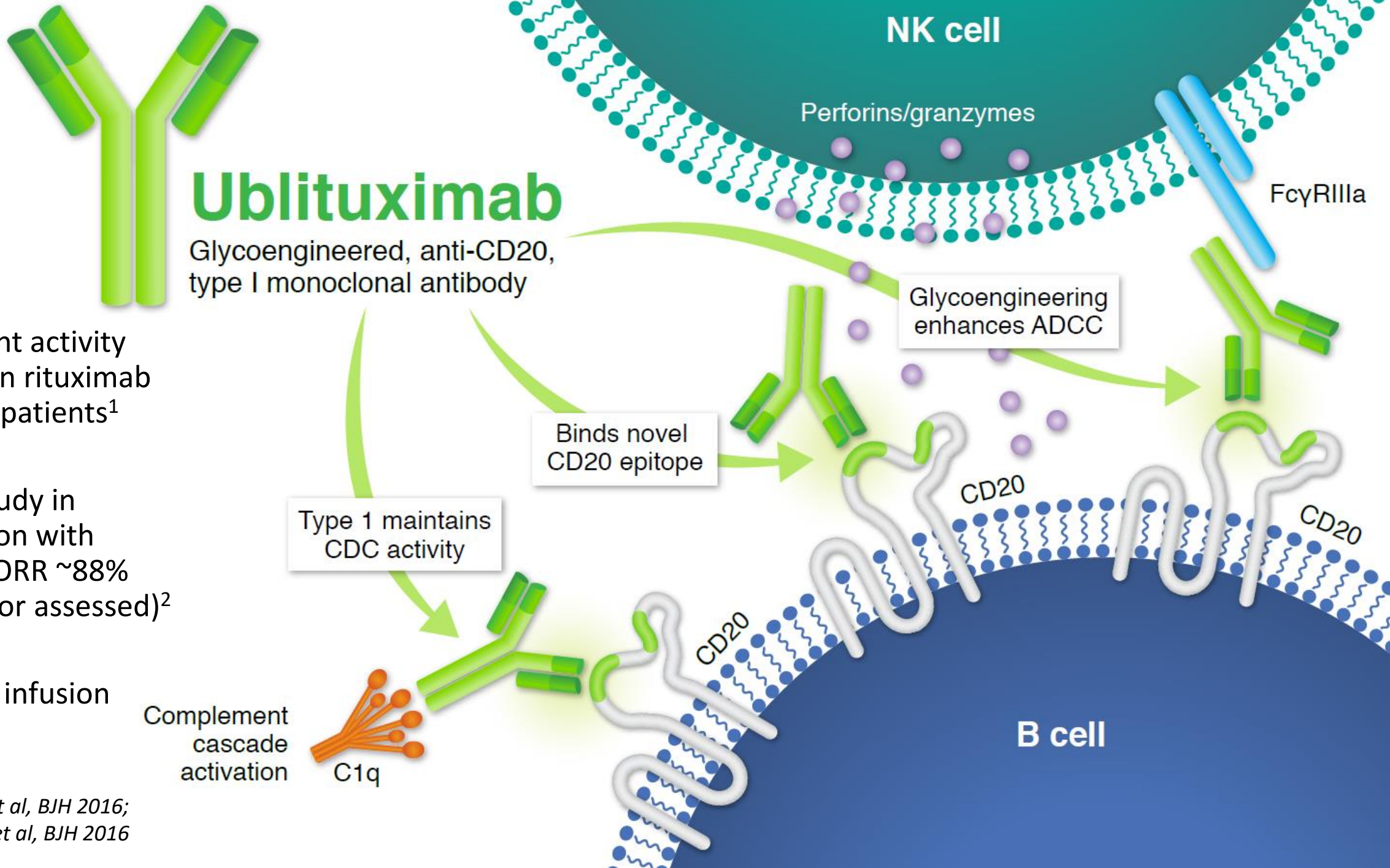
Introduction

- Despite the introduction of ibrutinib and other targeted agents, patients with CLL continue to relapse and complete remissions are rare
- Patients with high risk cytogenetic features still have the poorest outcome on ibrutinib
- Improving ibrutinib therapy through combinations remains a high priority



Byrd et al, Blood 2015

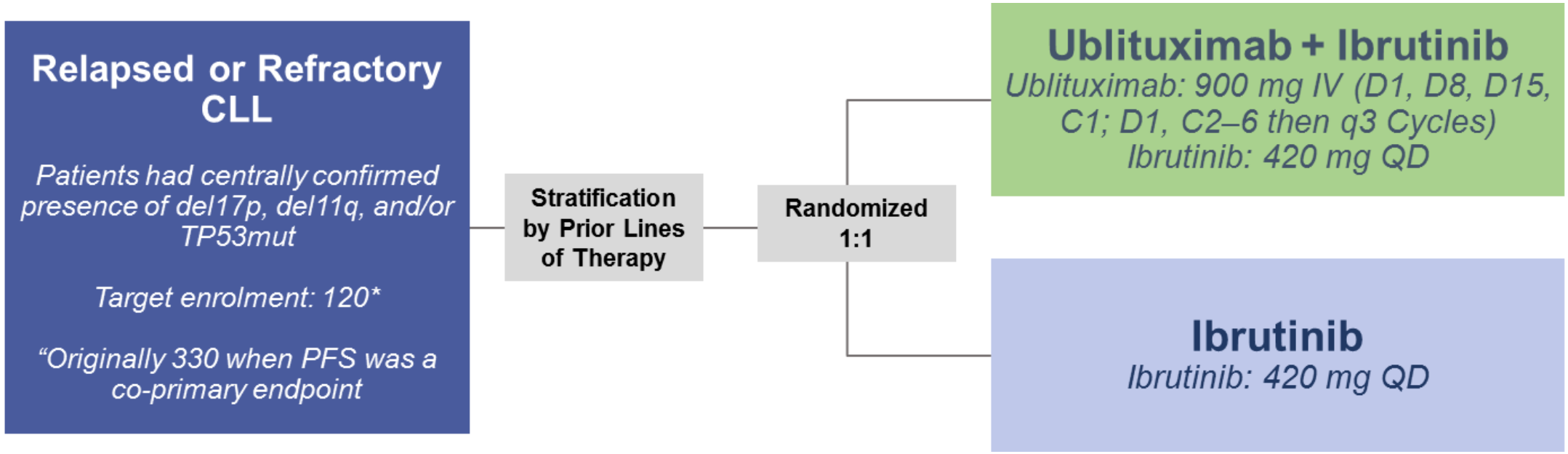


- Single agent activity observed in rituximab refractory patients[1]
- Phase 2 study in combination with ibrutinib: ORR ~88% (investigator assessed)[2]
- 90 minute infusion times

[1]O'Connor et al, BJH 2016;
[2]Sharman et al, BJH 2016

UTX-IB-301 (GENUINE) Study Design

- Open-label, multicenter, randomized, Phase III study in relapsed or refractory high-risk CLL
- Originally designed with ORR and PFS as co-primary endpoints
  - Due to enrollment challenges, lowered target enrollment 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
  - PFS, DOR, TTR
  - Safety

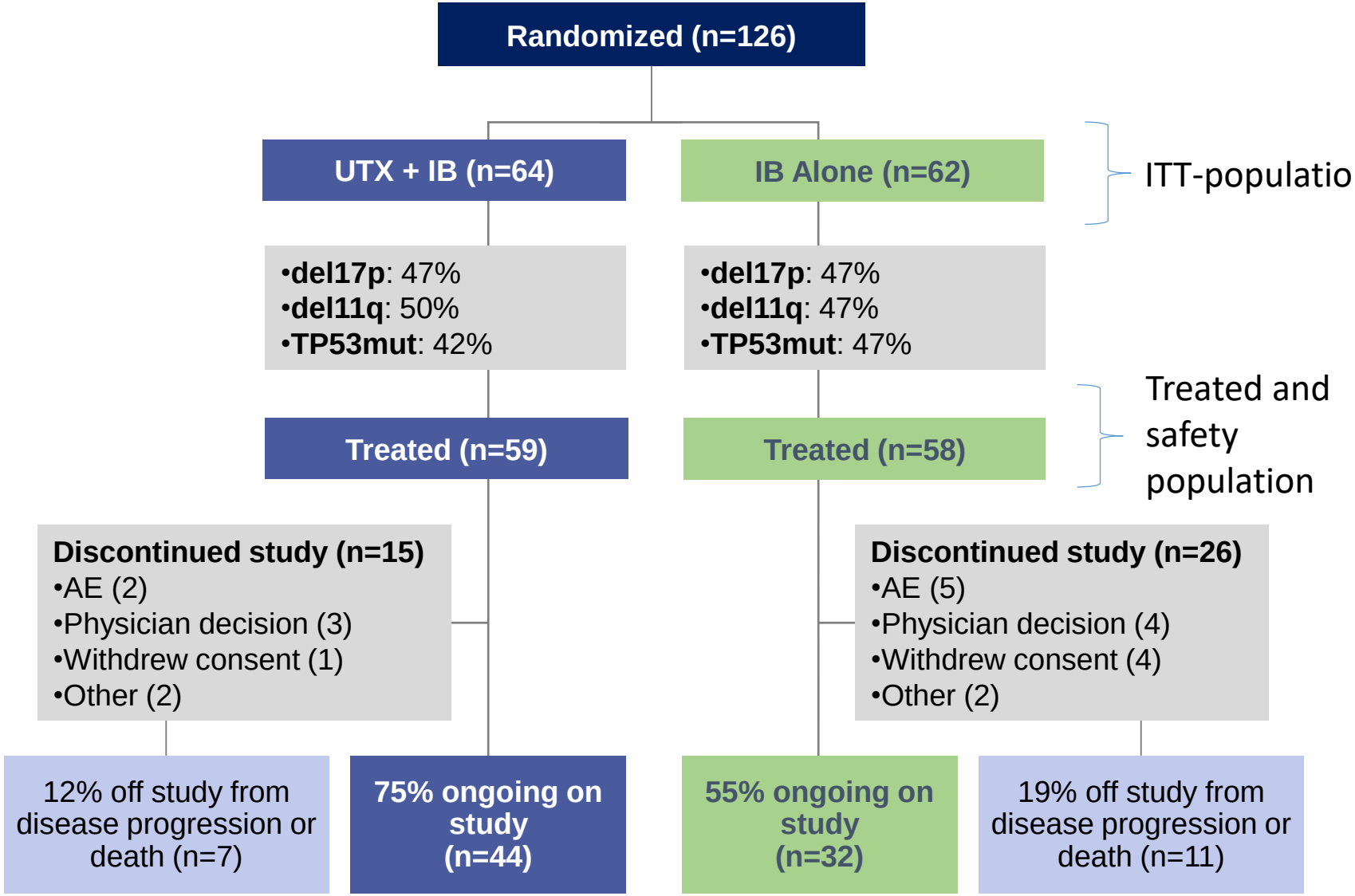
- **Statistical Assumptions:**
  - 120 patients required to have 90% power to detect an absolute difference in ORR of approximately 30%

Key Eligibility Criteria

- Age ≥18 y
- Relapsed/refractory CLL requiring treatment
  - Centrally confirmed presence of 17p del, 11q del, and/or TP53 mut
- 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 either:
  - del17p, del11q or TP53
- 64% of UTX + IB patients and 66% of IB Alone patients were del17p or TP53 mut
- 36% of UTX + IB patients and 34% of IB Alone patients were del11q only
- Median Follow up: 11.4 mo



Data Cutoff: February 15, 2017

Demographics

Characteristic, % (n)	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%)

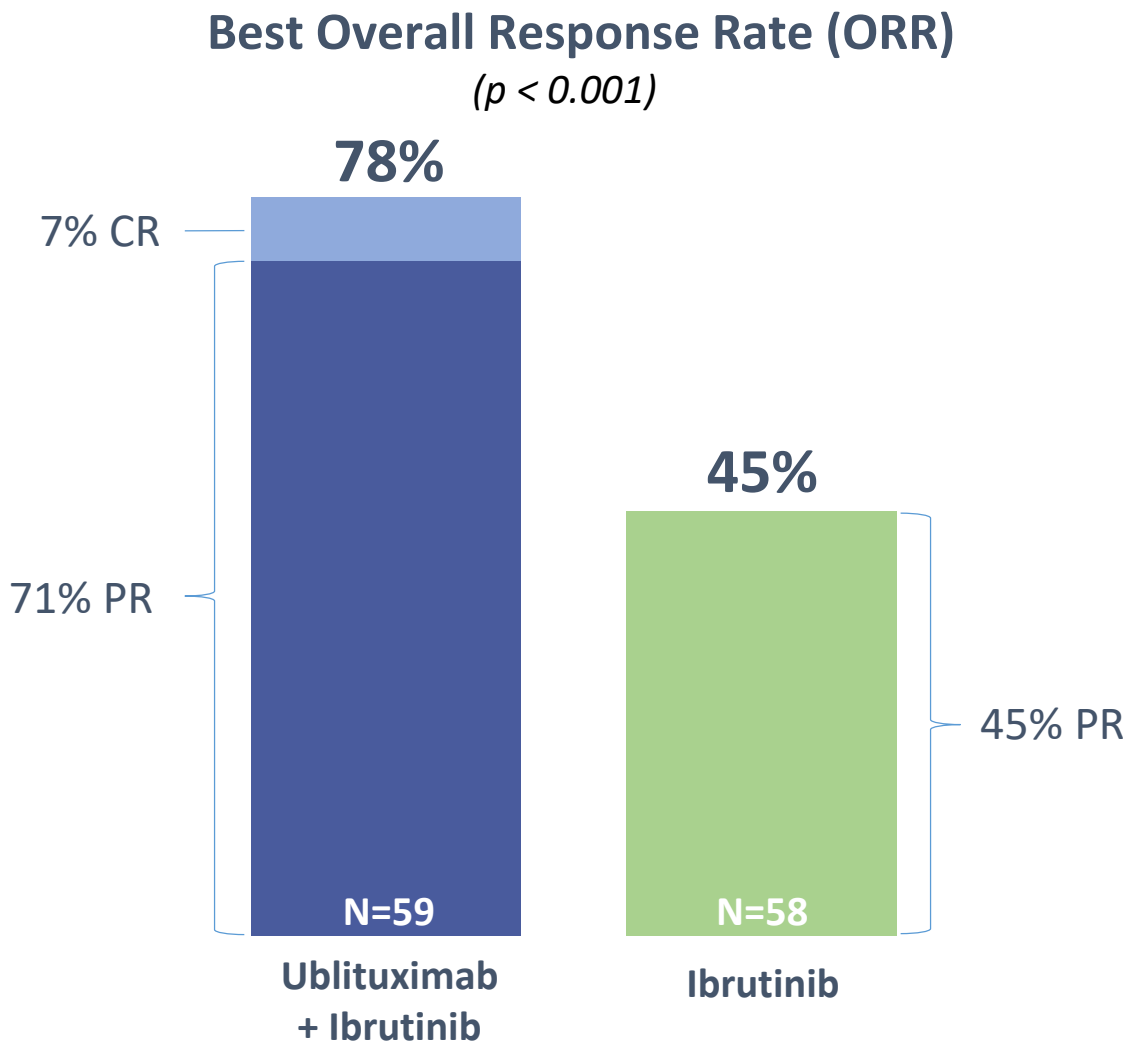
Safety: Adverse Event Summary (≥ 10%)

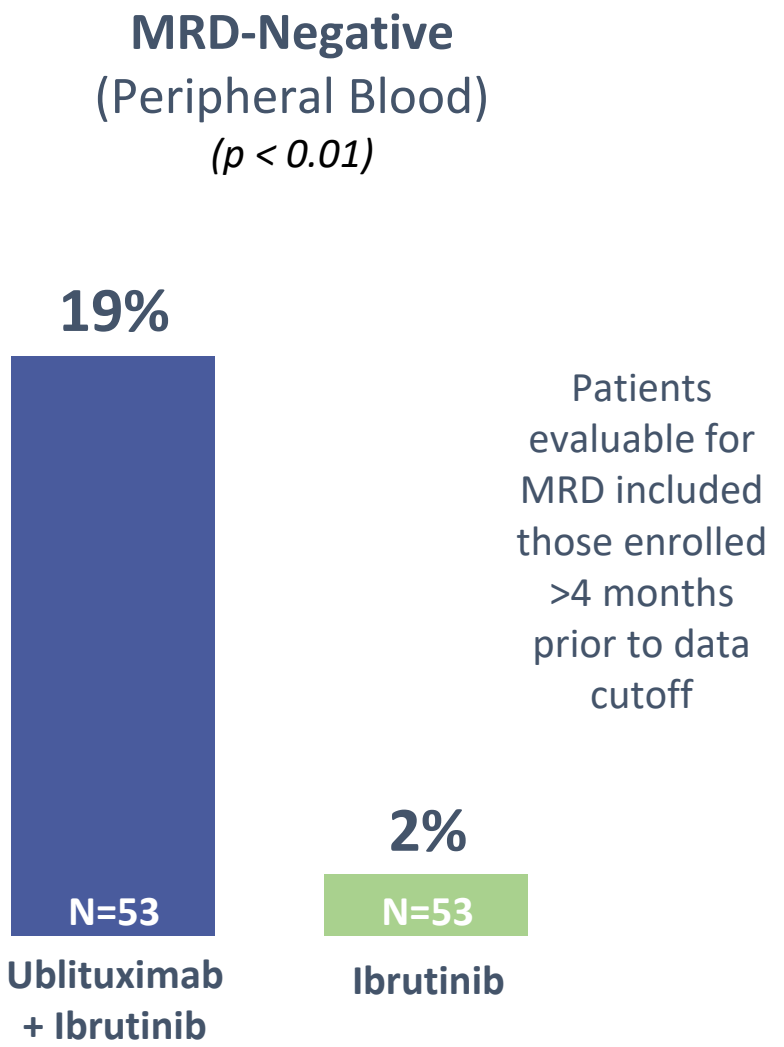
	Ublituximab + Ibrutinib (N=59)		Ibrutinib (N=58)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Infusion reaction	54%	5%	-	-
Diarrhea	42%	3%	40%	3%
Fatigue	27%	-	33%	2%
Insomnia	24%	-	10%	2%
Nausea	22%	-	21%	2%
Headache	20%	-	28%	2%
Arthralgia	19%	2%	17%	-
Cough	19%	-	24%	-
Abdominal Pain	15%	-	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%)	-

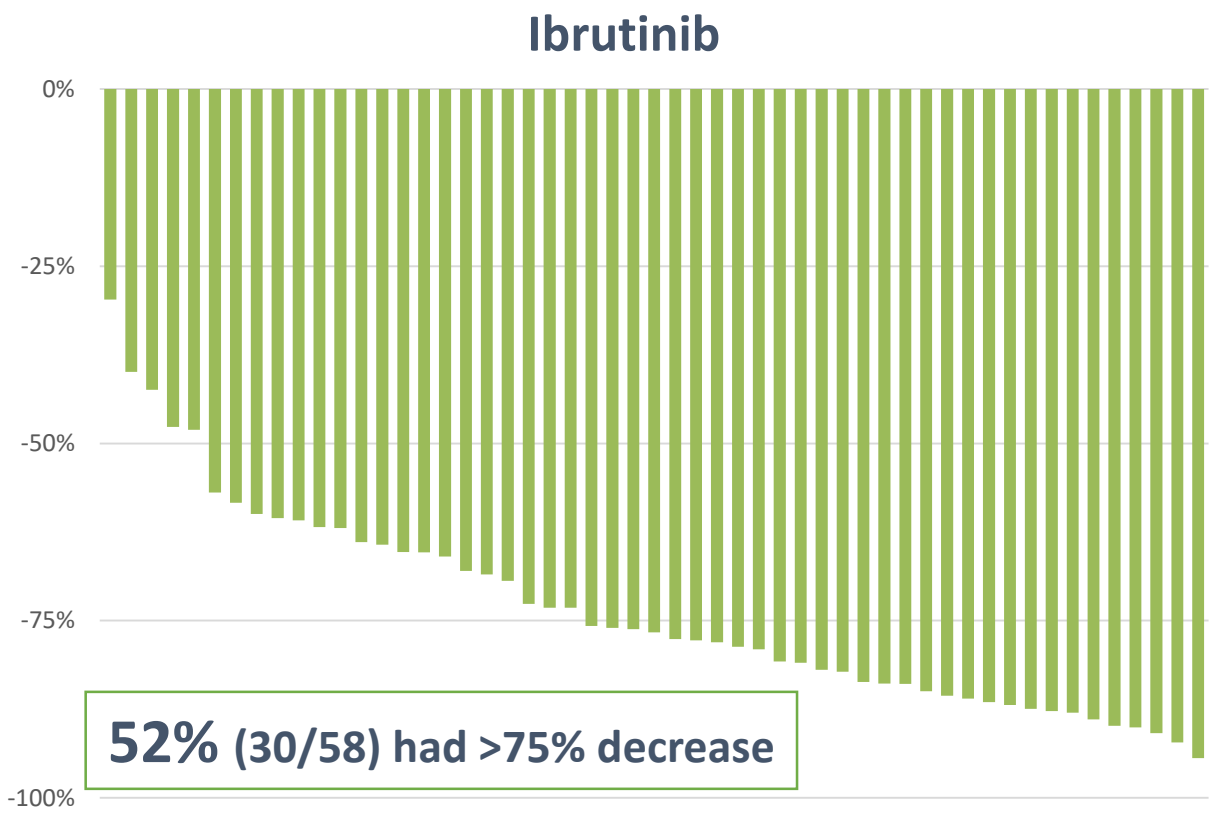
Efficacy: IRC Assessed ORR, CR, & MRD-Negativity

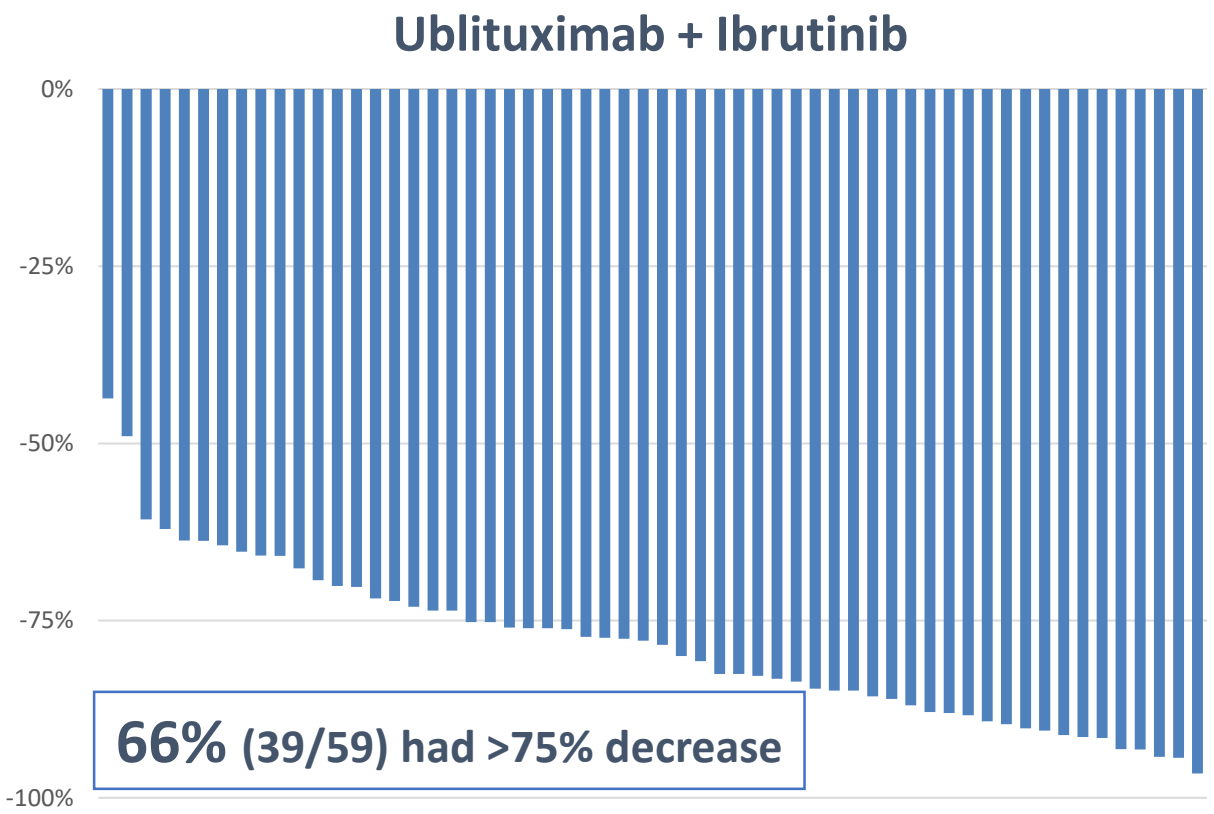




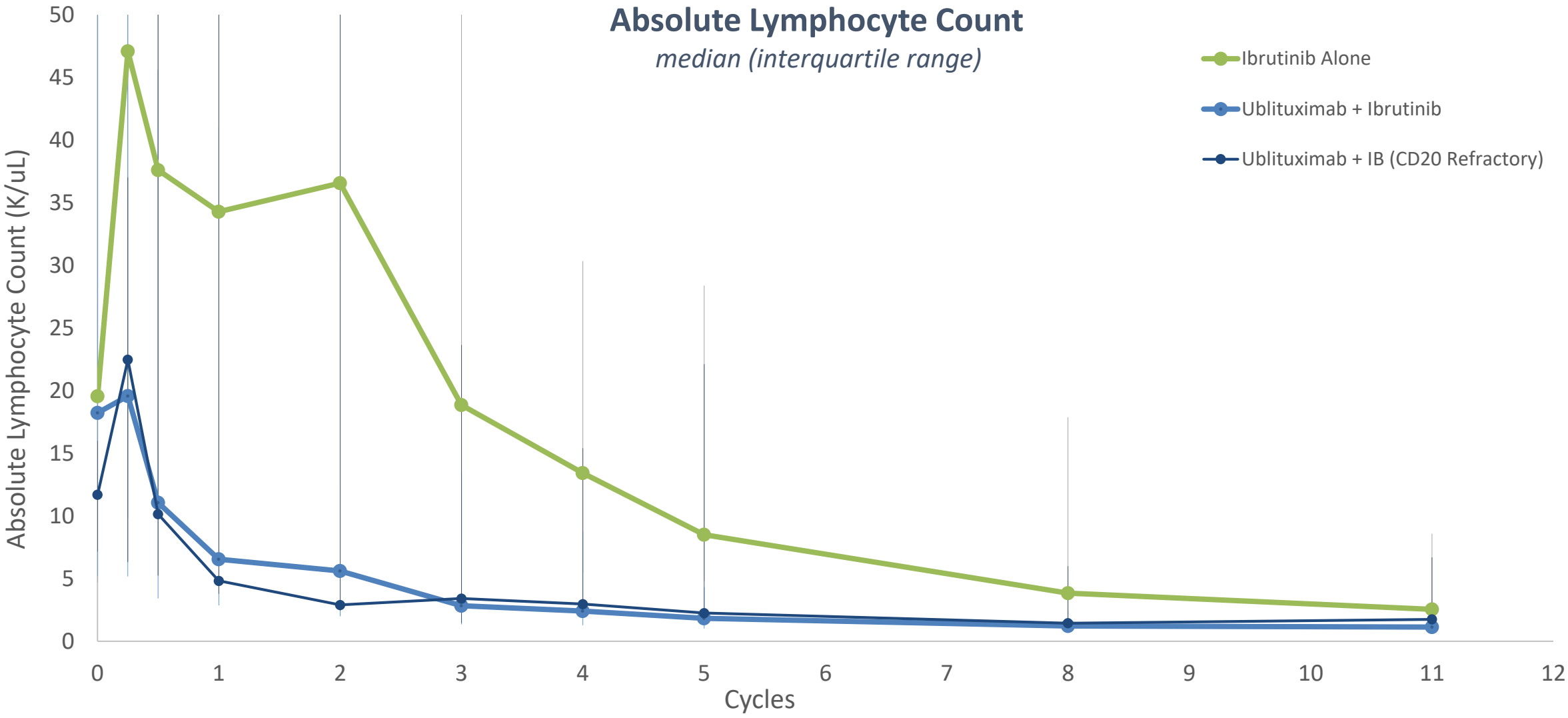
ITT ORR: p < 0.01

Best Percent Change in Nodal Size

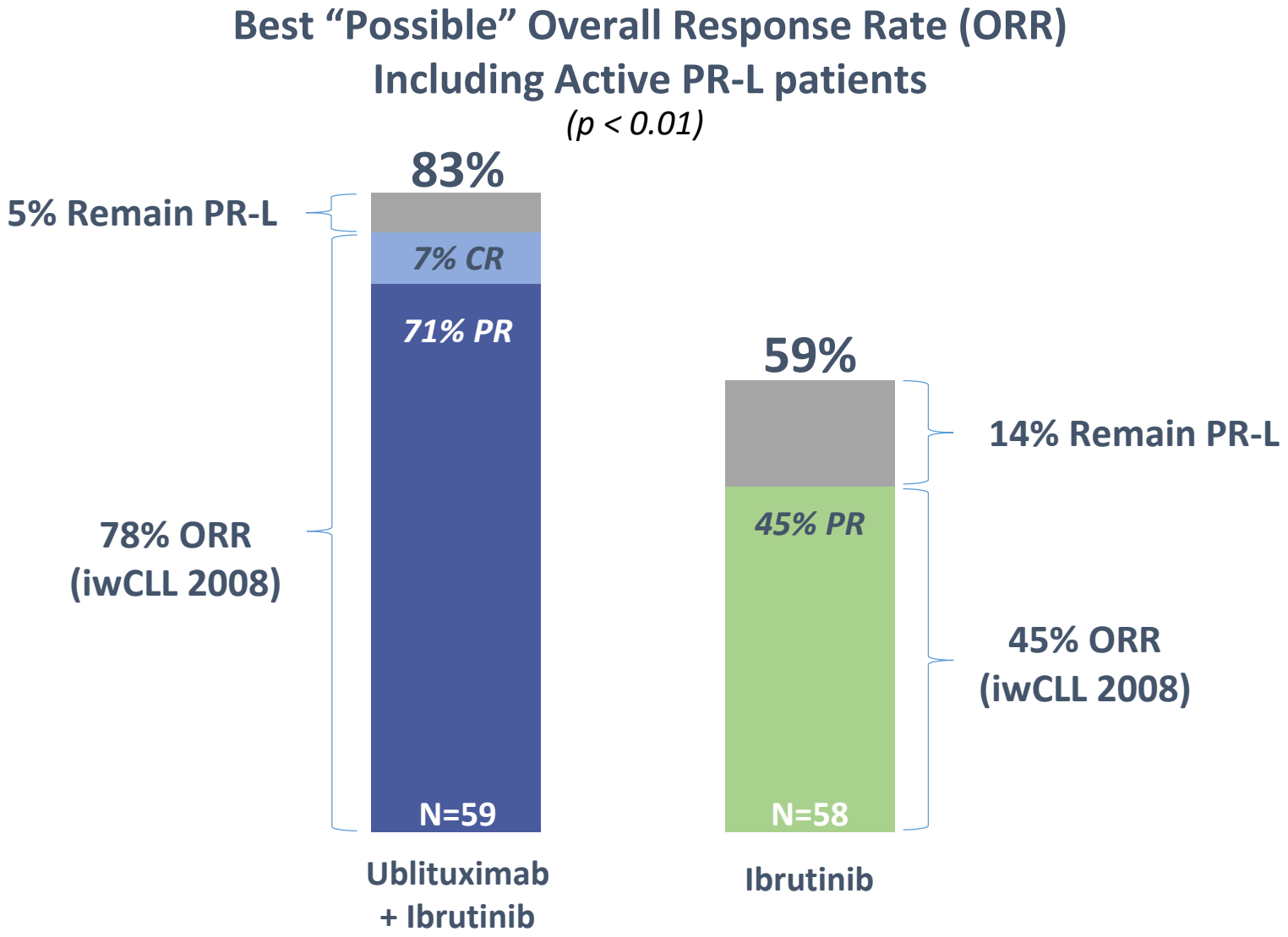




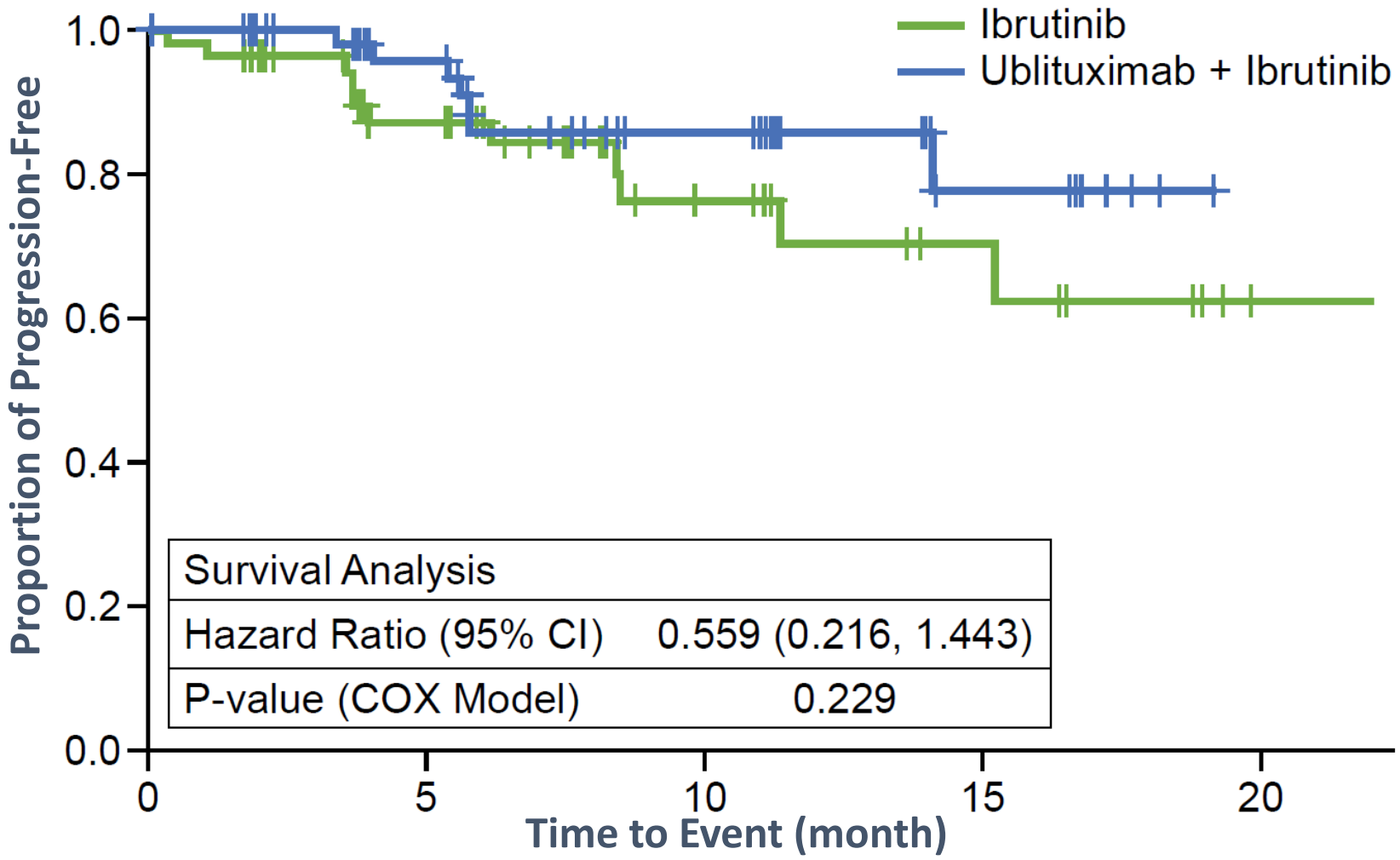
Lymphocytosis



Efficacy: Impact of including “PR-L” on ORR



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 ublituximab in combination with ibrutinib yields superior ORR to ibrutinib alone in high-risk CLL
  - ORR 45% (IB) vs. 78% (UTX+IB), $p<0.001$
  - CR rate 7% vs. 0 (secondary endpoint)
  - MRD- rate 19% vs 2% (secondary endpoint), $p<0.01$
- Secondary endpoint shows trend (HR=0.559) in improvement of PFS however not statistically significant at time of analysis
- With the exception of infusion related reactions, ublituximab did not alter the safety profile of ibrutinib monotherapy

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  - **USA**: Ian Flinn, Danielle Brander, Anthony Mato, Suman Kambhampati, John Burke, Frederick Lansigan, Marshall Schreeder, Scott Lunin, Alexander Zweibach, Jason Chandler, Mikhail Shtivelband, Nilanjan Ghosh, Patrick Travis, Bipin Amin, Charles Farber, David Wright, Habte Yimer, Herbert Eradat, Jason Melear, Jeff Sharman, John Pagel, Kenneth Miller, Michael Boxer, Michael Guarino, Mohit Narang, Noel Laudi, Russell Baur, Subhash Sharma, Thomas Sunnenberg, Vincent Hansen, Adam Olszewski, Andrew Bernstein, Anthony Gulati, Burke Brooks, David Riseberg, Dhatri Kodali, Gilles Lugassy, James Essell, Joseph Leach, Kathleen Phelan, Leonard Klein, Mazen Khalil, Nashat Gabrail, Ndegwa Njuguna, Robert Gordon, Robert Jacobson, Robert Siegel, Sharad Jain, Spencer Shao, Stefano Tarantolo, Sunil Babu, Suzanne Fanning, Yuvraj Choudhary. **ISRAEL**: Gilles Lugassy

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