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Chronic Lymphocytic Leukemia

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Disclosures

In compliance with ACCME policy, ASH requires disclosures to the session audience:

Speakers

Nitin Jain, MD

Disclosures

Consultancy: AbbVie; Adaptive Biotechnologies; ADC Therapeutics; AstraZeneca; Beigene; Bristol Myers Squibb; Cellectis; Eli Lilly; Genentech; Gilead; Ipsen; Janssen; Mei Pharma; MingSight; Novalgen; Pfizer; Pharmacyclics; Precision Biosciences; Servier

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Incyte; Kisoji Biotechnology; Medisix; MingSight; Newave; Novalgen; Novartis; Pfizer; Pharmacyclics; Precision Biosciences; Sana Biotechnology; Servier; Takeda; TransThera Sciences

Honoraria: AbbVie; Adaptive Biotechnologies; ADC Therapeutics; AstraZeneca; Beigene; Bristol Myers Squibb; Cellectis; Eli Lilly; Genentech; Gilead; Ipsen; Janssen; Mei Pharma; MingSight; Novalgen; Pfizer; Pharmacyclics; Precision Biosciences; Servier

Membership on a Board or Advisory Committee: AbbVie; Adaptive Biotechnologies; ADC Therapeutics; AstraZeneca; Beigene; Bristol Myers Squibb; Cellectis; Eli Lilly; Genentech; Gilead; Ipsen; Janssen; Mei Pharma; MingSight; Novalgen; Pfizer; Pharmacyclics; Precision Biosciences; Servier

Discussion of off-label drug use: N/A



Learning Objectives

Upon participation in this activity, attendees will be able to:

- Summarize clinical outcomes of ibrutinib and venetoclax combination therapy
- Compare ibrutinib and zanubrutinib safety and efficacy
- Discuss emerging therapies
 - After previous treatment with BTK and BCL2 inhibitors
 - In Richter transformation



Treatment Evolution in CLL

1960s

Alkylating agents
- Chlorambucil
- Cyclophosphamide

1970s

Purine nucleosides
- Fludarabine
- Pentostatin
- Cladribine

1980s

Purine nucleosides
and alkylators

1990s

**Chemoimmunotherapy
(FCR, BR)**
Alemtuzumab
Lenalidomide

2000s

2014-

BTK inhibitors (**Ibrutinib, Acalabrutinib**)
PI3K inhibitors (**Idelalisib, Duvelisib**)
BCL-2 inhibitor (**Venetoclax**)
Novel CD20 mAb (**Obinutuzumab**)

2023

BTK inhibitors
(**Zanubrutinib, Pirtobrutinib**)

2024+

CAR T, CD20 Bispecifics, others

Case #1

A 68-year-old man with a 2-year history of previously untreated CLL presents for follow-up. He complains of fatigue and an increase in the size of his lymph nodes. Labs show WBC 115 K/mcL (ALC 110 K/mcL, ANC 4.85 K/mcL), HGB 9.1 g/dL, platelets 218 K/mcL, β 2M 4.6 mg/L, LDH 302 U/L, and negative DAT. On physical exam, he has diffuse lymphadenopathy with the largest lymph node measuring 10 × 7 cm in the right axilla. His ECOG PS is 0. Prognostic markers at diagnosis were unmutated IGHV and del 11q22.3. Past medical history is significant for hypertension and hypothyroidism.



Question #1

What do you recommend for frontline therapy?

- A. FCR
- B. Ibrutinib
- C. Acalabrutinib +/- obinutuzumab
- D. Zanubrutinib
- E. Venetoclax and obinutuzumab
- F. Ibrutinib and venetoclax



Question #1

What do you recommend for frontline therapy?

- A. FCR
- B. Ibrutinib
- C. Acalabrutinib +/- obinutuzumab
- D. Zanubrutinib
- E. Venetoclax and obinutuzumab
- F. Ibrutinib and venetoclax

Abstracts

Phase 2 studies of ibr + ven

Phase 3 study of ibr + ven vs. chlorambucil + obinutuzumab





Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) 4-Year Follow-up Data

Nitin Jain, Michael Keating, Philip Thompson, Alessandra Ferrajoli, Jayastu Senapati, Jan Burger, Gautam Borthakur, Koichi Takahashi, Zeev Estrov, Koji Sasaki, Tapan Kadia, Marina Konopleva, Yesid Alvarado, Musa Yilmaz, Courtney DiNardo, Prithviraj Bose, Maro Ohanian, Naveen Pemmaraju, Elias Jabbour, Rashmi Kanagal-Shamanna, Keyur Patel, Wei Wang, Jeffrey Jorgensen, Sa Wang, Sameh Nassar, Naveen Garg, Hyunsoo Hwang, Xuemei Wang, Nichole Cruz, Ana Ayala, William Plunkett, Hagop Kantarjian, Varsha Gandhi, William Wierda

Department of Leukemia
The University of Texas MD Anderson Cancer Center
ASH 2022, Abstract 95

Ibrutinib and Venetoclax Trial

- Investigator-initiated Phase II trial (NCT02756897)
- Patients with treatment-naïve CLL/SLL meeting 2008 iwCLL treatment criteria with at least one of the following feature:
 - Del(17p) or mutated *TP53*
 - Del(11q)
 - Unmutated *IGHV*
 - Age ≥ 65 years

Jain N et al. N Engl J Med. 2019 May 30;380(22):2095-2103.
Jain N et al. JAMA Oncol. 2021 Aug 1;7(8):1213-1219.

Treatment Schema

	C1	C2	C3	C4 --> 27 (<u>24 cycles</u> of Combined Rx)
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

Duration of therapy: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx

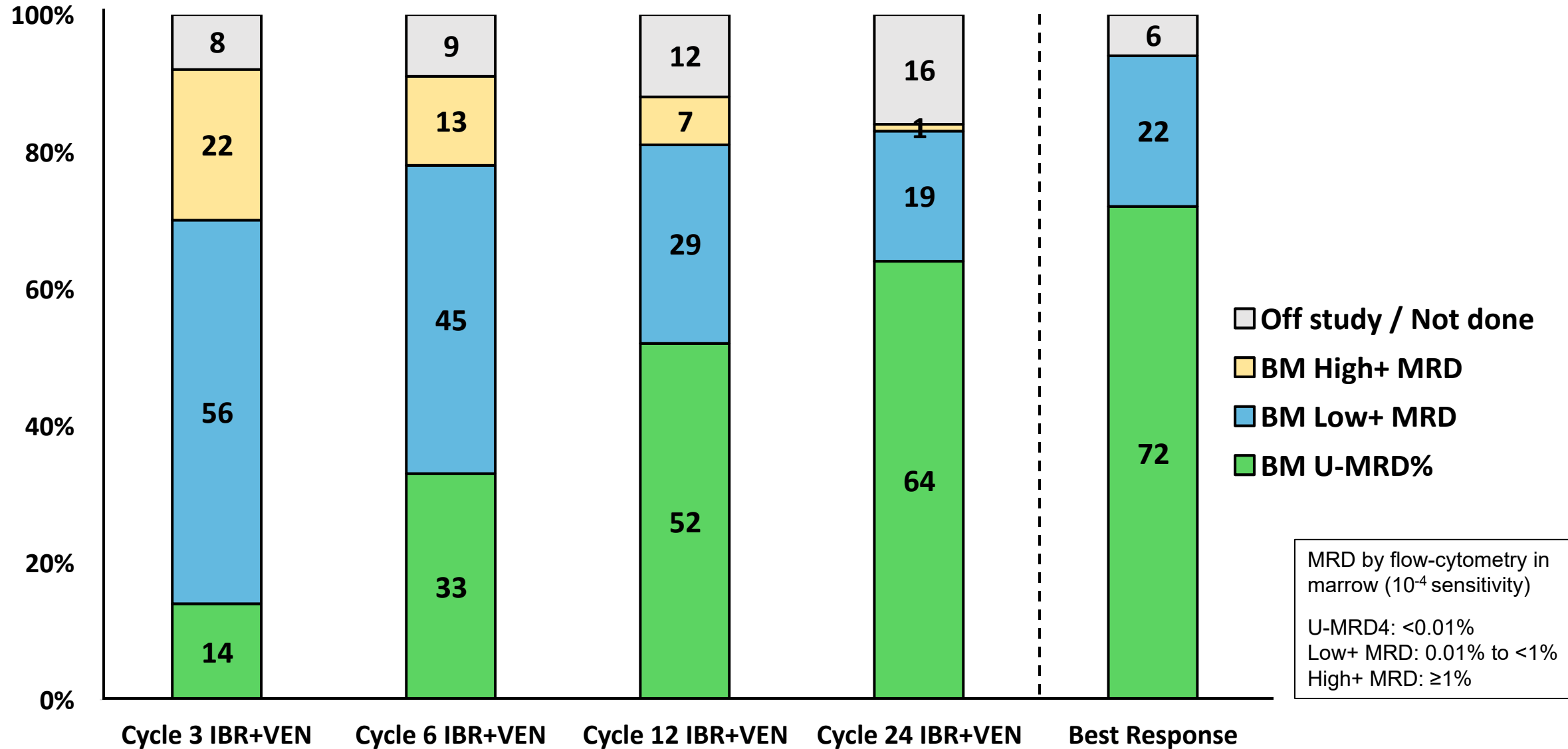
- Negative (<0.01%): Stop both IBR and VEN
- Positive ($\geq 0.01\%$): Continue 12 additional cycles of IBR + VEN

Baseline Characteristics (N=120)

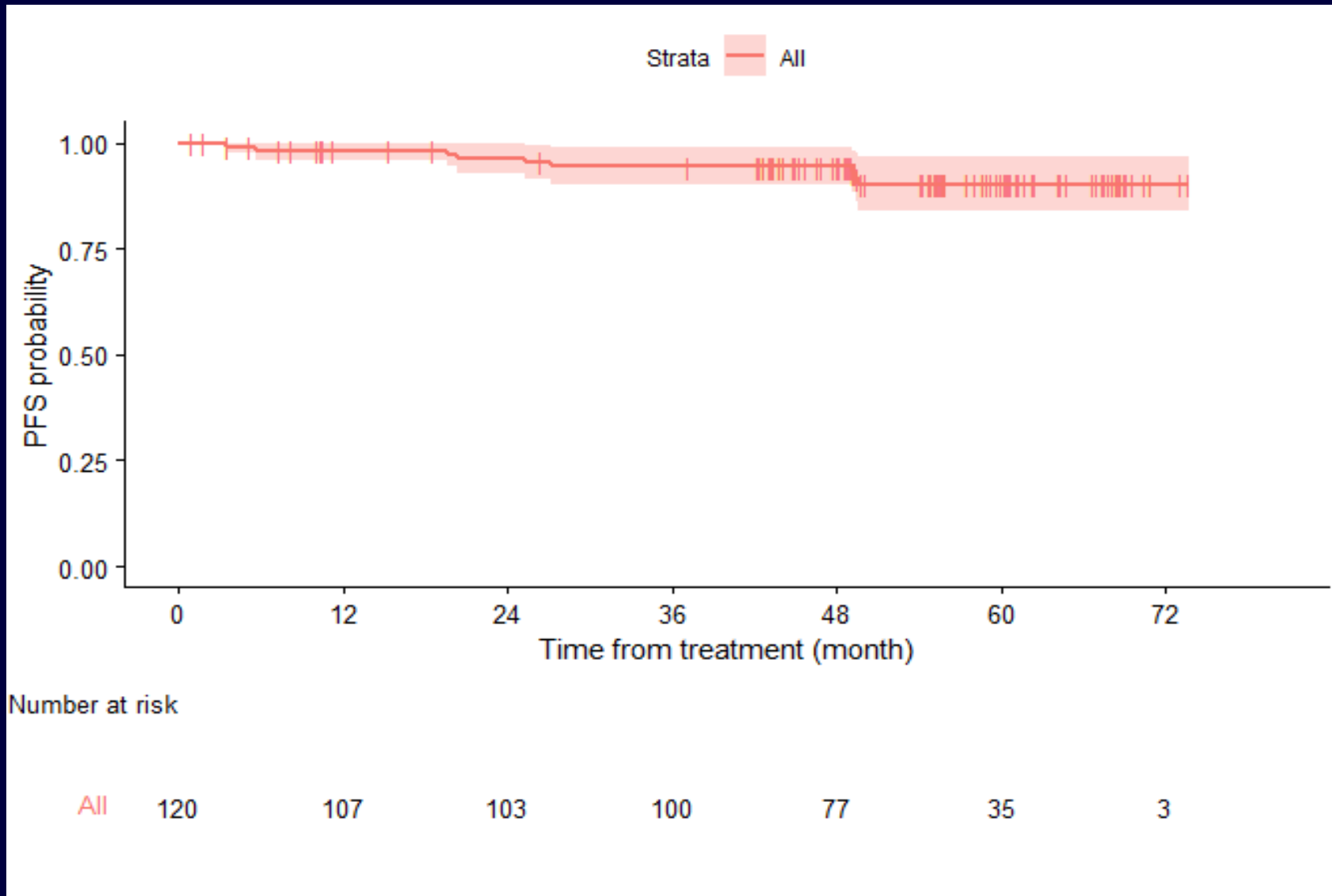
Between August 2016
and February 2019,
120 pts were enrolled

		n (%) or median [range]
Age, years		64.5 [26-88]
	≥65	60 (50)
	≥70	35 (29)
Gender, M		87 (73)
ALC, K/ μ L		76.3 [1.14-366]
PLT, K/ μ L		140 [28-334]
HGB, g/dL		12.0 [7.7-18.4]
B2M, mg/L		3.6 [1.7-13.7]
FISH	Del(17p)	20 (17)
	Del(11q)	31 (26)
	Trisomy 12	23 (19)
	Negative	19 (16)
	Del(13q)	27 (22)
<i>IGHV</i> status (n=116)	Unmutated	100 (86)
Cytogenetics (n=115)	Complex	15 (13)
Mutations (n=119)	<i>TP53</i>	19 (16)
	<i>NOTCH1</i>	35 (29)
	<i>SF3B1</i>	26 (22)
	<i>BIRC3</i>	10 (8)
Del(17p) / <i>TP53</i> -m		27 (23)

Marrow MRD Response at Serial Time-Points Intent-to-Treat (N=120)

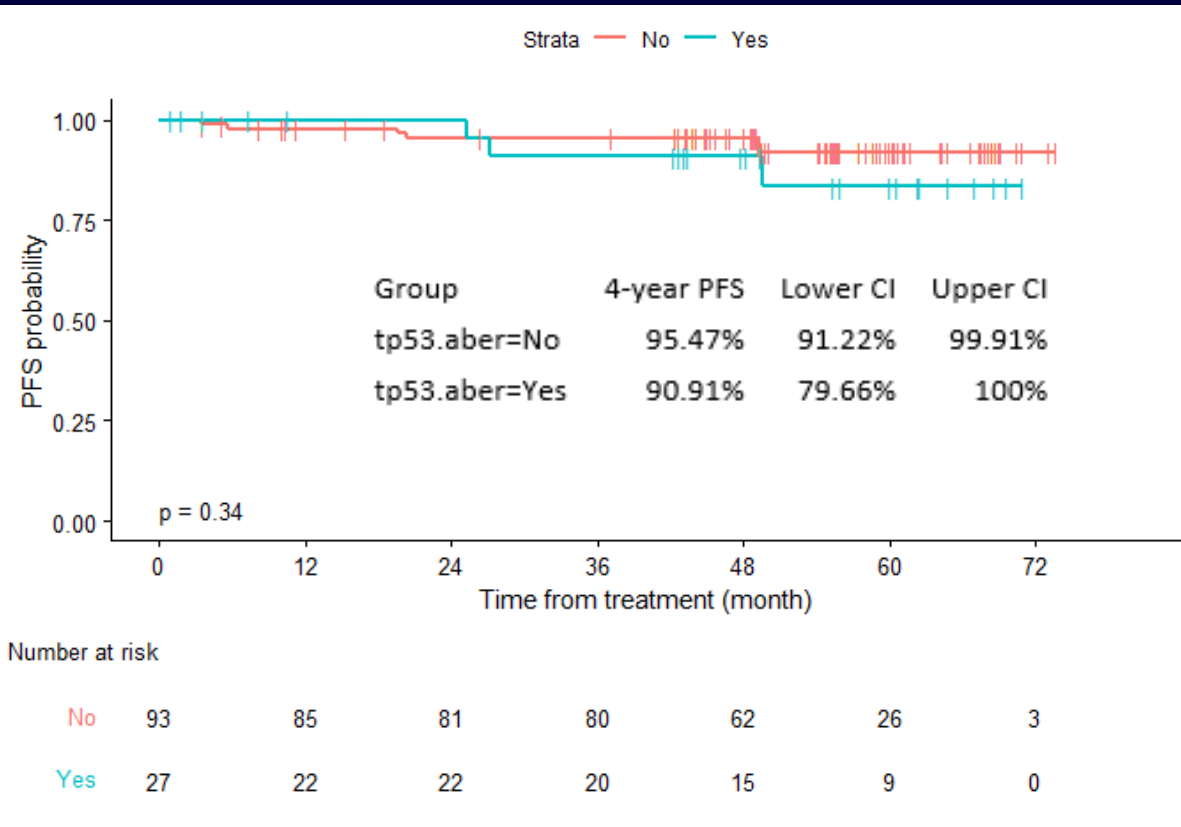


PFS for all Patients (N=120)

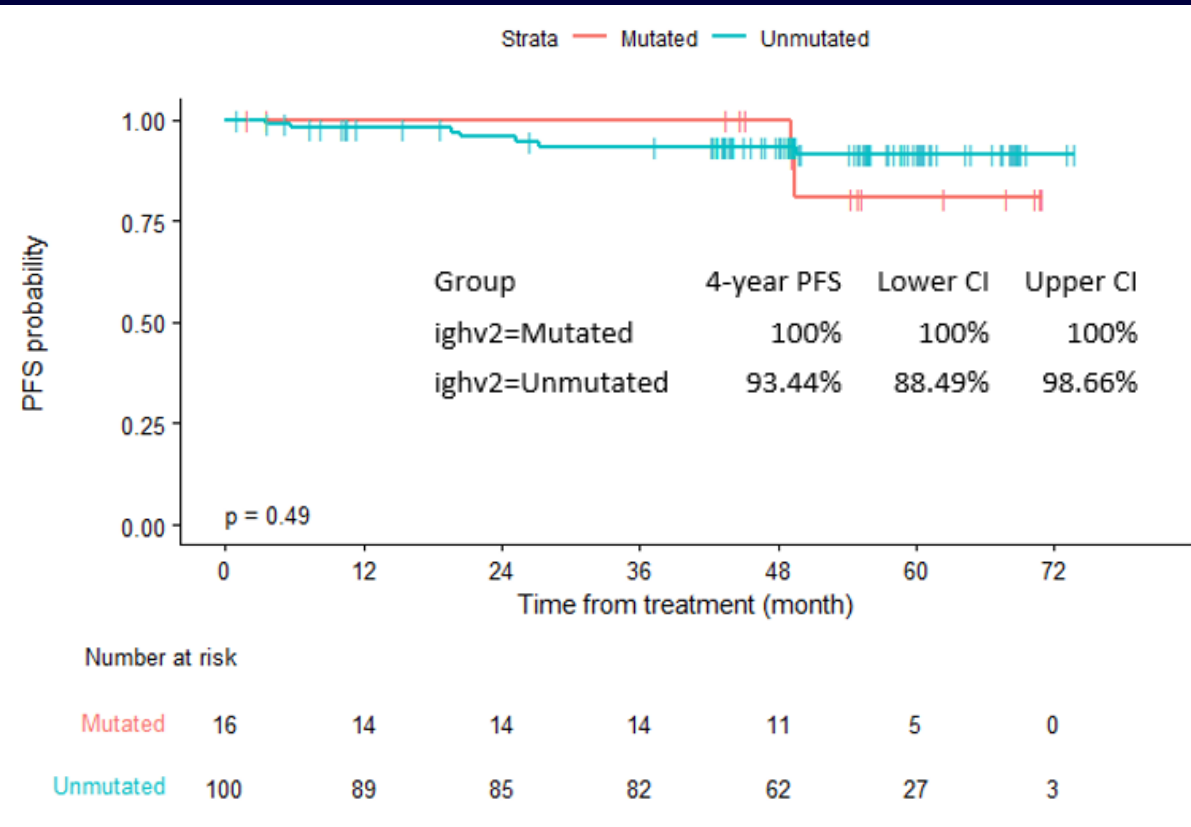


4-year PFS = 94.5%
(95% CI, 90.3-98.9%)

PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

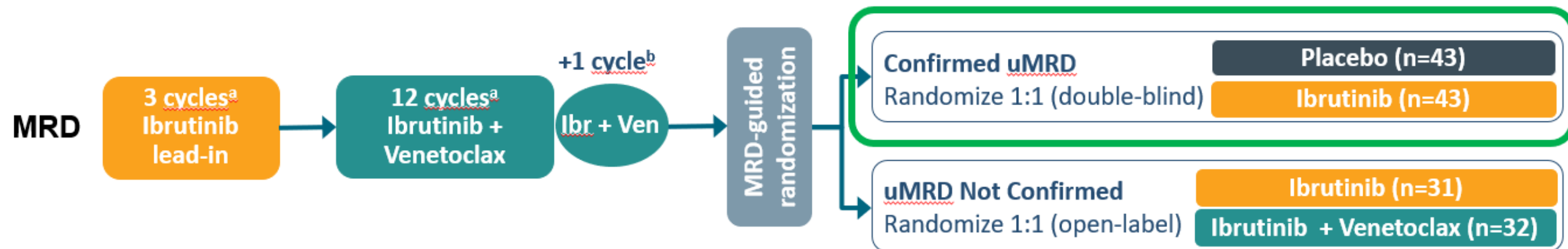
Treatment Outcomes After Undetectable MRD With First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed-Duration Treatment (Placebo) Versus Continued Ibr With Up to 5 Years Follow-up in the CAPTIVATE Study

John N. Allan, MD¹; Tanya Siddiqi, MD²; Thomas J. Kipps, MD, PhD³; Bryone J. Kuss, MBBS, PhD, FRACP, FRCPA⁴; Xavier C. Badoux, MBBS, FRACP, FRCPA⁵; Alessandra Tedeschi, MD⁶; Jacqueline C. Barrientos, MD, MS⁷; Stephen Opat, FRACP, FRCPA, MBBS⁸; Ian W. Flinn, MD, PhD⁹; Eva Gonzalez Barca, MD, PhD¹⁰; Ryan Jacobs, MD¹¹; Edith Szafer-Glusman, PhD¹²; Cathy Zhou, MS¹²; Anita Szoke, MD¹²; William G. Wierda, MD, PhD¹³; Paolo Ghia, MD, PhD¹⁴; Constantine S. Tam, MBBS, MD¹⁵

¹Weill Cornell Medicine, New York, NY, USA; ²City of Hope National Medical Center, Duarte, CA, USA; ³UC San Diego Moores Cancer Center, San Diego, CA, USA; ⁴Flinders University and Medical Center, Bedford Park, SA, Australia; ⁵Ministry of Health, Kogarah, NSW, Australia; ⁶ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; ⁷Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, USA; ⁸Monash University, Clayton, VIC, Australia; ⁹Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; ¹⁰Institut Catalá d'Oncologia Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; ¹¹Levine Cancer Institute, Charlotte, NC, USA; ¹²Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA; ¹³Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁴Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; ¹⁵The Alfred Hospital and Monash University, Melbourne, VIC, Australia.

CAPTIVATE MRD Cohort Study Design

- CAPTIVATE (NCT02910583) is an international, multicenter phase 2 study evaluating first-line treatment with the Ibr + Ven combination
- The CAPTIVATE study comprises 2 cohorts: FD¹ and MRD²
- In this MRD cohort, after completion of Ibr + Ven, patients with Confirmed uMRD* were randomly assigned to double-blind treatment with placebo (ie, a fixed-duration regimen), or continued ibrutinib



*Confirmed uMRD was defined as uMRD serially over at least 3 cycles in both peripheral blood and bone marrow. Patients who achieved Confirmed uMRD with Ibr + Ven were randomly assigned 1:1 to double-blinded treatment with placebo or single-agent ibrutinib.

^aOne cycle = 28 days; ^bDuring MRD status confirmation and tumor response assessment; FD, fixed duration; MRD, minimal residual disease.

1. Tam CS et al. *Blood*. 2022;139:3278-3289. 2. Wierda, WG. *J Clin Oncol*, 2021;39:3853-3865.

ASH 2022; Allan JN et al.

Patient Disposition, Confirmed uMRD

- Median time on study was 56 months (ibrutinib arm range, 25–68 months; placebo arm range, 40–65 months), with a median of 41 months post-randomization

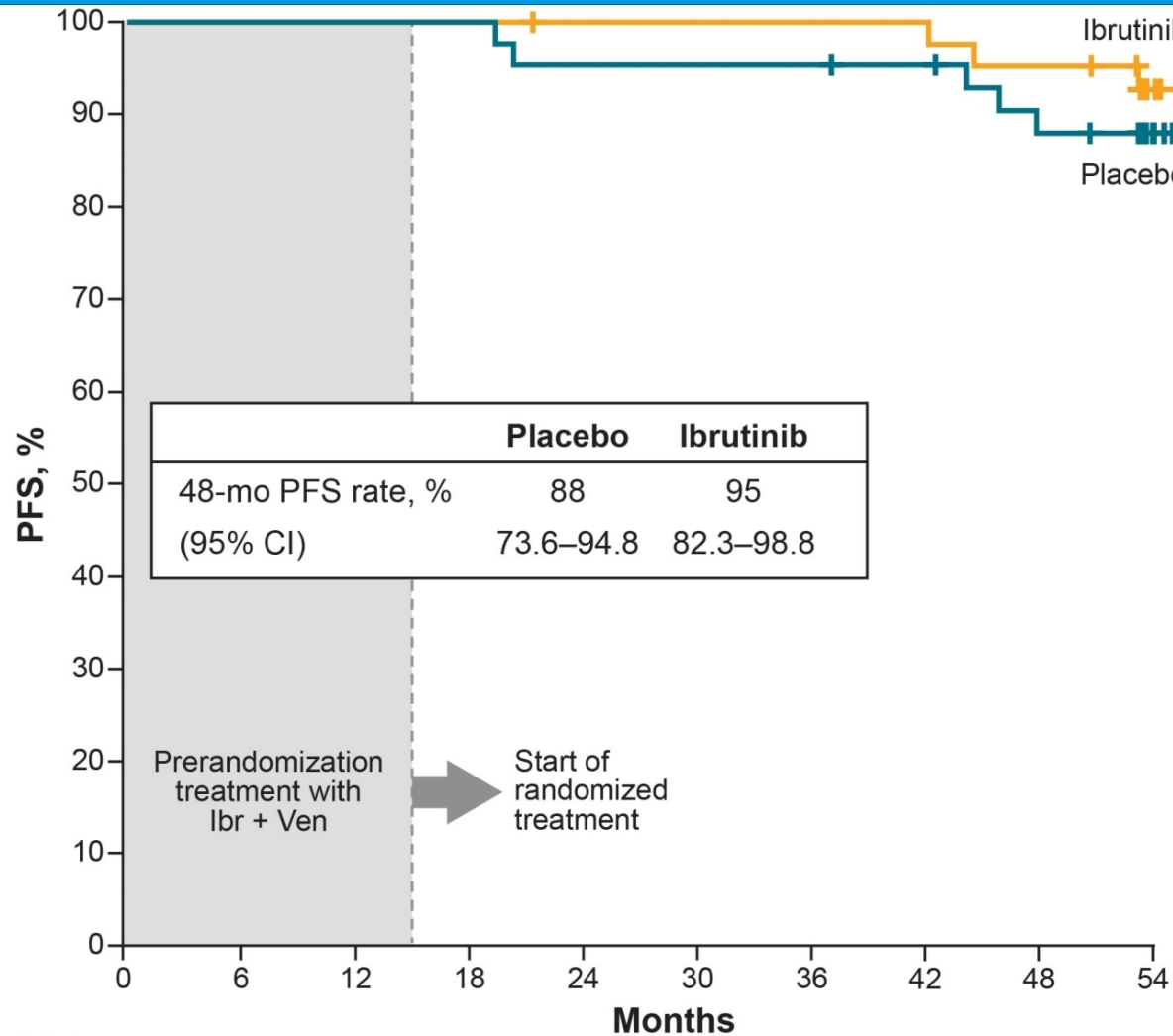
Characteristic	All treated patients N=164	Confirmed uMRD n=86	
		Placebo n=43	Ibrutinib n=43
Median age (range), years	58 (28–69)	61 (43–69)	56 (34–69)
High genomic risk features, n (%)			
Unmutated IGHV	99 (60)	30 (70)	30 (70)
del(17p)/TP53 mutation	32 (20)	2 (5)	13 (30)
Complex karyotype ^a	31 (19)	4 (9)	13 (30)
del(11q) ^b	28 (17)	8 (19)	10 (23)

- Full baseline demographics and disease characteristics were reported previously¹



^aDefined as ≥ 3 abnormalities by conventional CpG-stimulated cytogenetics. ^bWithout del(17p) per Dohner hierarchy.
1. Wierda WG. *J Clin Oncol*. 2021;39:3853-3865.

Progression-Free Survival Rates Continue to Be High and Durable Across Study Arms



- At 48 months, PFS was 88% (95% CI, 74–95) with placebo and 95% (95% CI, 82–99) with continued ibrutinib

PD and Retreatment Outcomes

- 3 of 7 patients with PD in the placebo arm have initiated retreatment with ibrutinib; all 3 patients had PR
- 2 patients in the ibrutinib arm had PD; none have initiated retreatment

Patients at risk		0	6	12	18	24	30	36	42	48	54
1	Ibrutinib	43	43	43	43	42	42	42	42	40	26
	Placebo	43	43	43	43	41	41	41	40	36	22

Residual Disease Kinetics Among Patients With High-Risk Factors Treated With First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): the GLOW Study

Carsten U. Niemann, MD, PhD,¹ Talha Munir, MBBS,² Carol Moreno, MD,³ Carolyn Owen, MD,⁴ George A. Follows, PhD,⁵ Ohad Benjamini, MD,⁶ Ann Janssens, MD, PhD,⁷ Mark-David Levin, MD, PhD,⁸ Tadeusz Robak, MD, PhD,⁹ Martin Šimkovič, MD, PhD,¹⁰ Sergey Voloshin, MD, PhD,¹¹ Vladimir I. Vorobyev, PhD,¹² Munci Yagci, MD,¹³ Loic Ysebaert, MD, PhD,¹⁴ Keqin Qi, PhD,¹⁵ Qianya Qi, PhD,¹⁶ Lori Parisi, MPH,¹⁶ Srimathi Srinivasan, PhD,¹⁷ Natasha Schuier, MD,¹⁸ Kurt Baeten, PhD¹⁹, Angela Howes, PhD²⁰, Donne Bennett Caces, MD, PhD¹⁶, and Arnon P. Kater, MD, PhD²¹

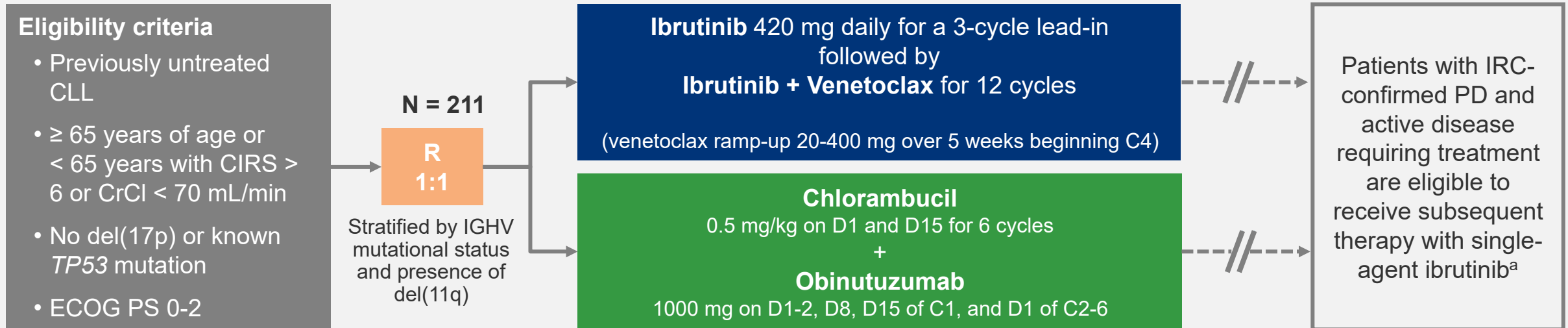
¹Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; ²St James's Hospital, Leeds, UK; ³Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Josep Carreras Leukaemia Research Institute, Barcelona, Spain; ⁴Tom Baker Cancer Centre, Calgary, Canada; ⁵Addenbrookes Hospital, Cambridge, UK; ⁶Sheba Medical Center, Ramat Gan, Israel; ⁷UZ Leuven Gasthuisberg, Leuven, Belgium; ⁸Albert Schweitzer hospital, Dordrecht, Netherlands; ⁹Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; ¹⁰University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; ¹¹Russian Scientific and Research Institute of Hematology and Transfusiology, St Petersburg, Russia; ¹²S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; ¹³Gazi Universitesi Tip Fakultesi, Ankara, Turkey; ¹⁴Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; ¹⁵Janssen Research & Development, Titusville, NJ; ¹⁶Janssen Research & Development, Raritan, NJ; ¹⁷Oncology Translational Research, Janssen Research & Development, Lower Gwynedd Township, PA; ¹⁸Janssen Research & Development, Dusseldorf, Germany; ¹⁹Janssen Research & Development, Beerse, Belgium; ²⁰Janssen Research & Development, High Wycombe, UK; ²¹Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Netherlands

<https://www.congresshub.com/Oncology/ASH2022/Ibrutinib/Niemann>

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Phase 3 GLOW Study (NCT03462719)



- **Primary end point: IRC-assessed PFS**
- Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety
- Current analysis
 - Median study follow-up of 46 months (range, 1.7-51.7)
 - MRD assessed in peripheral blood in responders by NGS

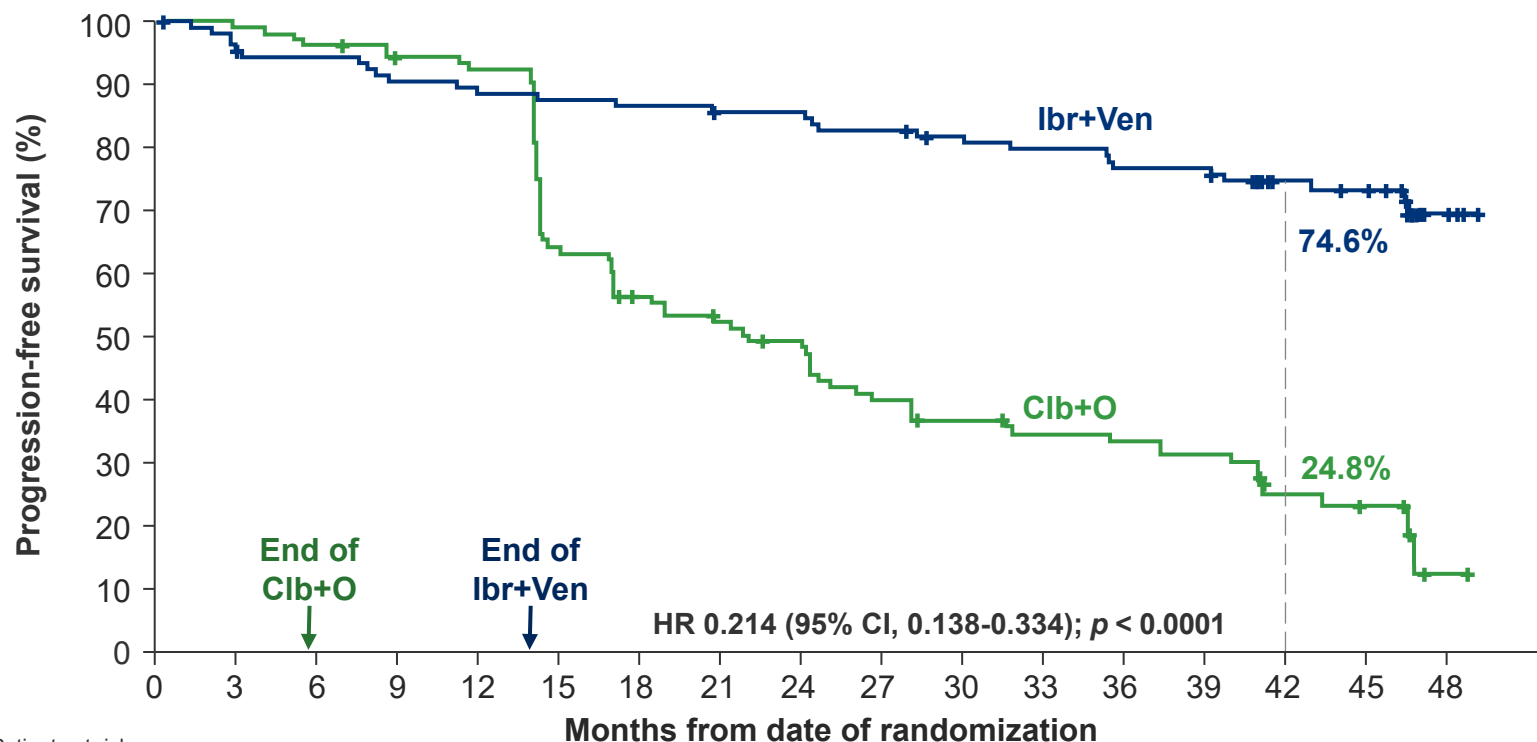
^aIbrutinib provided by the Sponsor to patients from both arms who were eligible to participate in the Subsequent Therapy Phase of the study.

C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease; NGS, next-generation sequencing.



GLOW: Progression-Free Survival by IRC Remained Superior For Ibr+Ven Versus Clb+O With 4 Years of Study Follow-up

Progression-Free Survival (IRC)



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
Ibr+Ven	106	98	98	94	92	91	90	88	87	85	80	79	76	74	52	48	2
Clb+O	105	104	101	97	95	65	56	50	43	38	34	31	30	28	14	12	1

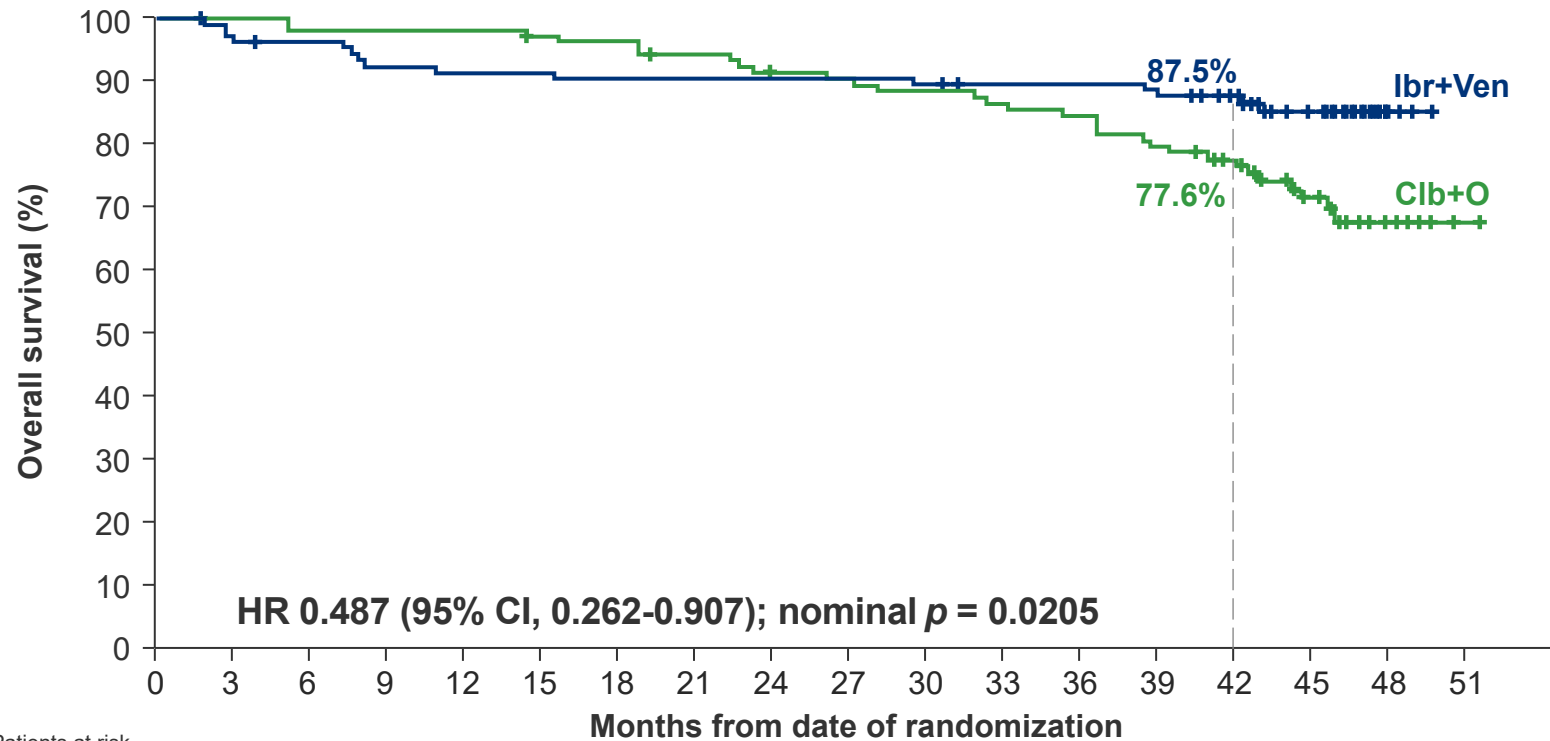
Median study follow-up: 46 months

- Ibr+Ven reduced the risk of progression or death by 79% versus Clb+O
 - HR 0.214 (95% CI, 0.138-0.334); $p < 0.0001$
- Estimated 3.5-year PFS rates:
 - 74.6% for Ibr+Ven
 - 24.8% for Clb+O



GLOW: Ibr+Ven Improved Overall Survival Versus Clb+O With 4 Years of Study Follow-up

Overall Survival (ITT)



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Ibr+Ven	106	101	100	96	95	95	94	94	94	94	93	91	91	90	83	57	12	0
Clb+O	105	105	103	103	103	101	100	97	93	92	90	88	86	81	74	47	15	1

Median study follow-up: 46 months

- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Causes of Death

n (%)	Ibr+Ven (N = 106)	Clb+O (N = 105)
PD	1 (0.9)	2 (1.9)
Infections	4 (3.8)	11 (10.5)
Other ^a	10 (9.4)	17 (16.2)
TOTAL	15 (14.2)	30 (28.6)

^aCause and number (Ibr+Ven arm, Clb+O arm) of "other" deaths: general/unknown (4, 5), cardiac (2, 4), central nervous system (2, 3), neoplasm (1, 3), euthanasia (1, 0), hepatobiliary (0, 1), respiratory (0, 1). ITT, intent to treat; BTKi, Bruton's tyrosine kinase inhibitor; PD, progressive disease; HR hazard ratio; CI, confidence interval.





Zanubrutinib Demonstrates Superior Progression-Free Survival Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Results from Final Analysis of ALPINE Randomized Phase 3 Study

Jennifer R. Brown, MD, PhD¹, Barbara Eichhorst, MD², Peter Hillmen, MD PhD³, Nicole Lamanna, MD⁴, Susan M. O'Brien, MD⁵, Constantine S. Tam, MBBS, MD^{6,7}, Lugui Qiu, MD⁸, Maciej Kaźmierczak, MD, PhD⁹, Wojciech Jurczak, MD, PhD¹⁰, Keshu Zhou, MD, PhD¹¹, Martin Simkovic MD, PhD^{12,13}, Jiri Mayer, MD¹⁴, Amanda Gillespie-Twardy, MD¹⁵, Alessandra Ferrajoli, MD¹⁶, Peter S. Ganly, BMBCh, PhD¹⁷, Robert Weinkove, MBBS, PhD^{18,19}, Sebastian Grosicki, MD, PhD²⁰, Andrzej Mital, MD, PhD²¹, Tadeusz Robak, MD, PhD²², Anders Osterborg, MD, PhD^{23,24}, Habte A. Yimer, MD²⁵, Tommi Salmi, MD²⁶, Megan (Der Yu) Wang, PharmD²⁶, Lina Fu, MS²⁶, Jessica Li, MS²⁶, Kenneth Wu, PhD²⁶, Aileen Cohen, MD, PhD²⁶, Mazyar Shadman, MD, MPH^{27,28}

¹Dana-Farber Cancer Institute, Boston, MA, USA; ²University of Cologne, Cologne, Germany; ³St James's University Hospital, Leeds, United Kingdom; ⁴Columbia University, New York, NY, USA; ⁵University of California, Irvine, CA, USA; ⁶The Alfred Hospital, Melbourne, Victoria, Australia; ⁷Monash University, Melbourne, Victoria, Australia; ⁸National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; ⁹Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; ¹⁰Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; ¹¹Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; ¹²4th Department of Internal Medicine - Hematology, University Hospital, Hradec Kralove, Czech Republic; ¹³Faculty of Medicine, Charles University, Prague, Czech Republic; ¹⁴Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; ¹⁵Blue Ridge Cancer Care, Roanoke, VA, USA; ¹⁶Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁷Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; ¹⁸Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, Wellington, New Zealand; ¹⁹Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; ²⁰Department of Hematology and Cancer Prevention, Health Sciences Faculty, Medical University of Silesia, Katowice, Poland; ²¹Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland; ²²Medical University of Lodz, Lodz, Poland; ²³Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; ²⁴Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; ²⁵Texas Oncology-Tyler/US Oncology Research, Tyler, TX, USA; ²⁶BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; ²⁷Fred Hutchinson Cancer Center, Seattle, WA, USA; ²⁸University of Washington, Seattle, WA, USA



ALPINE Study Design

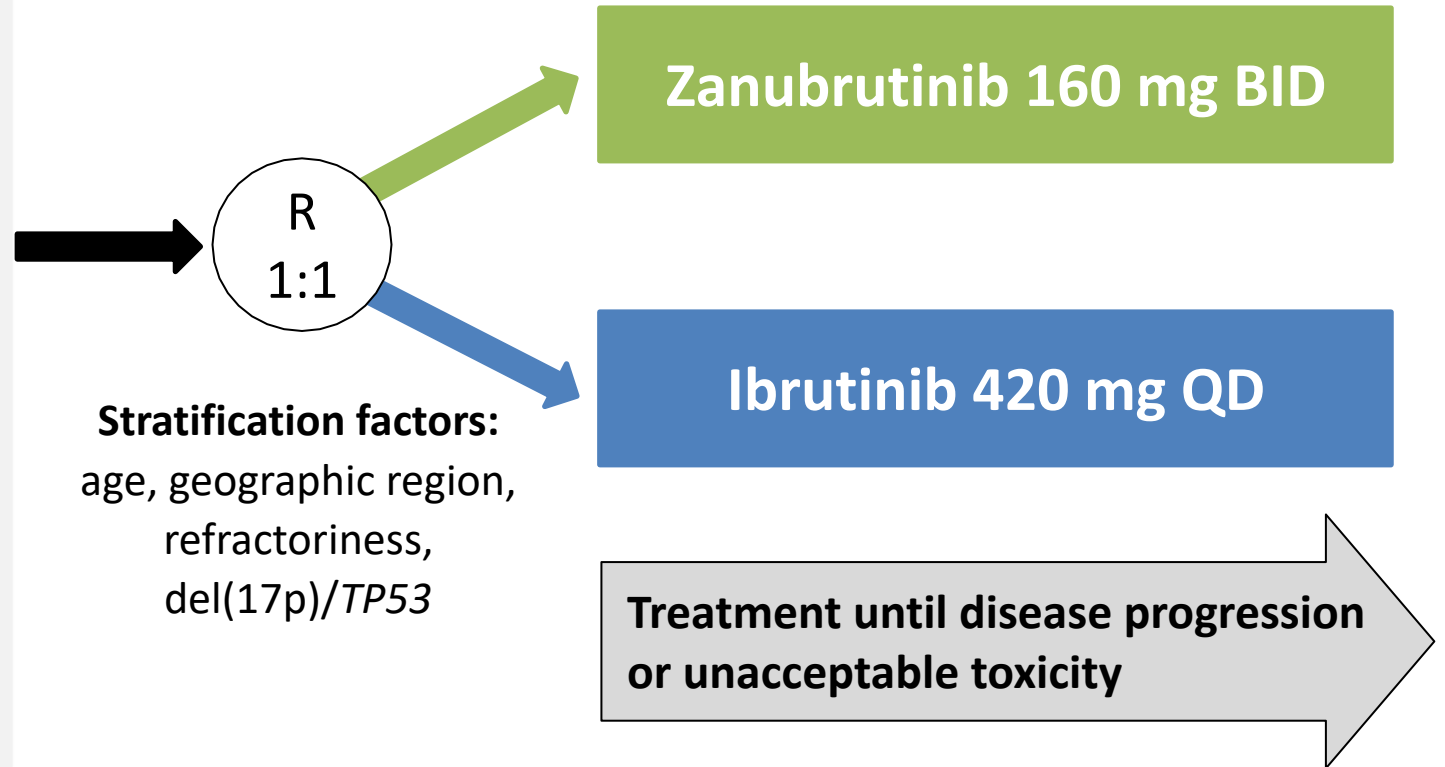
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥ 1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

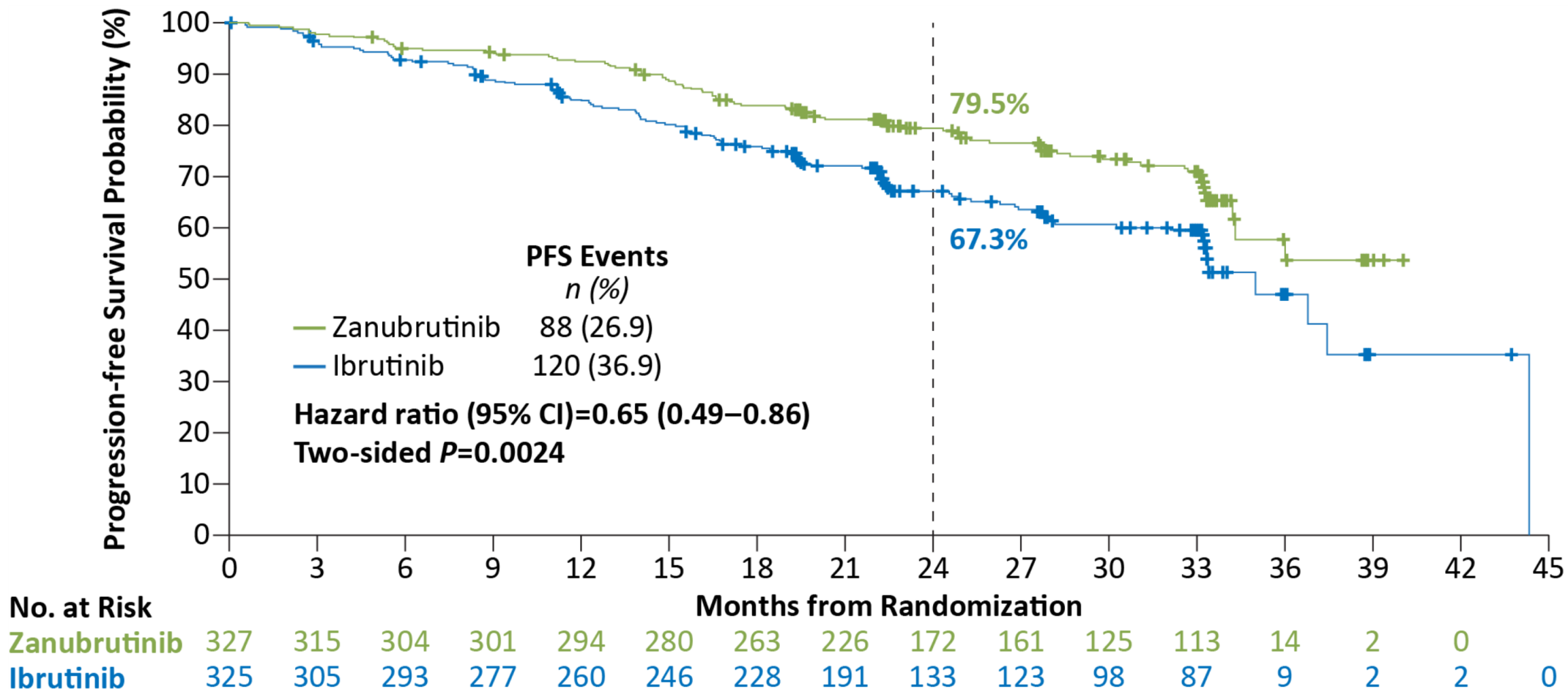
Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



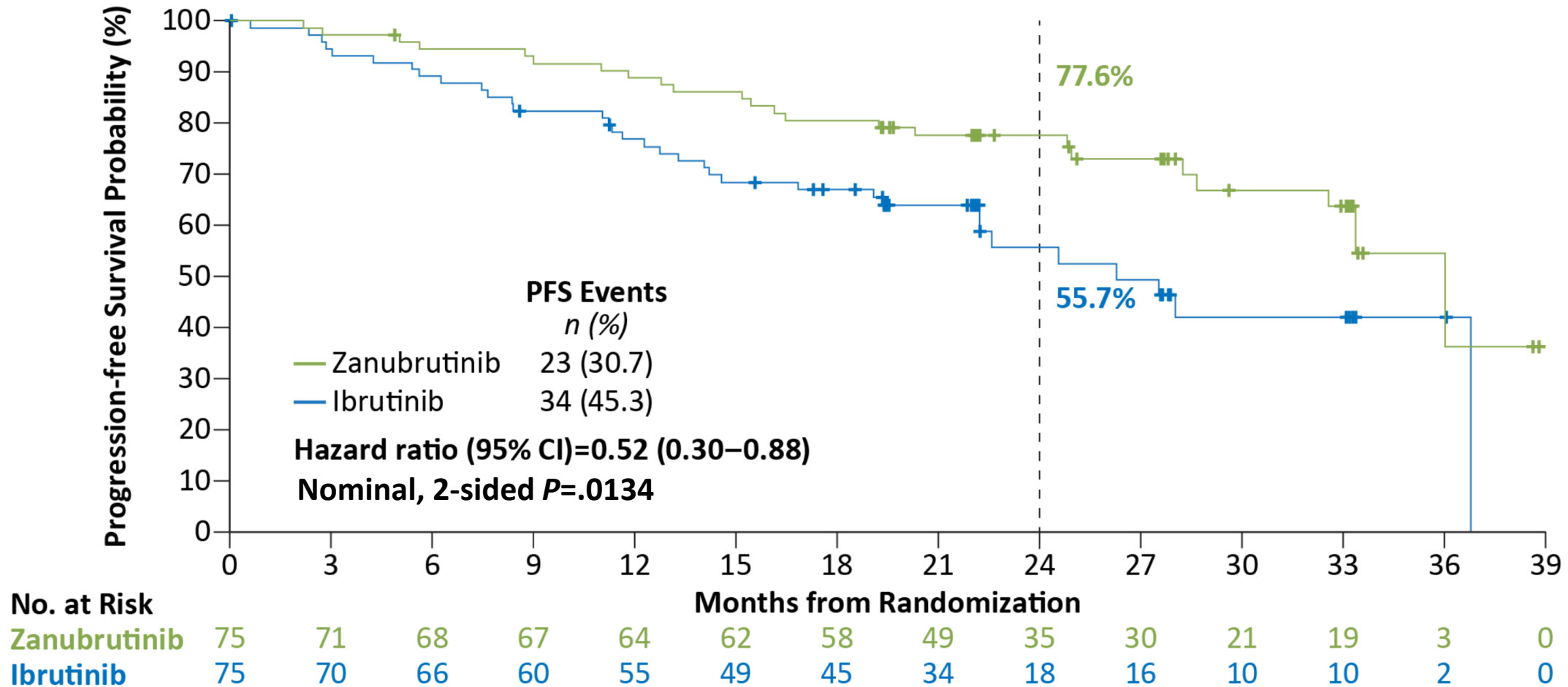
Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Data cutoff: 8 Aug 2022

Zanubrutinib Improved PFS in Patients with del(17p)/TP53^{mut}

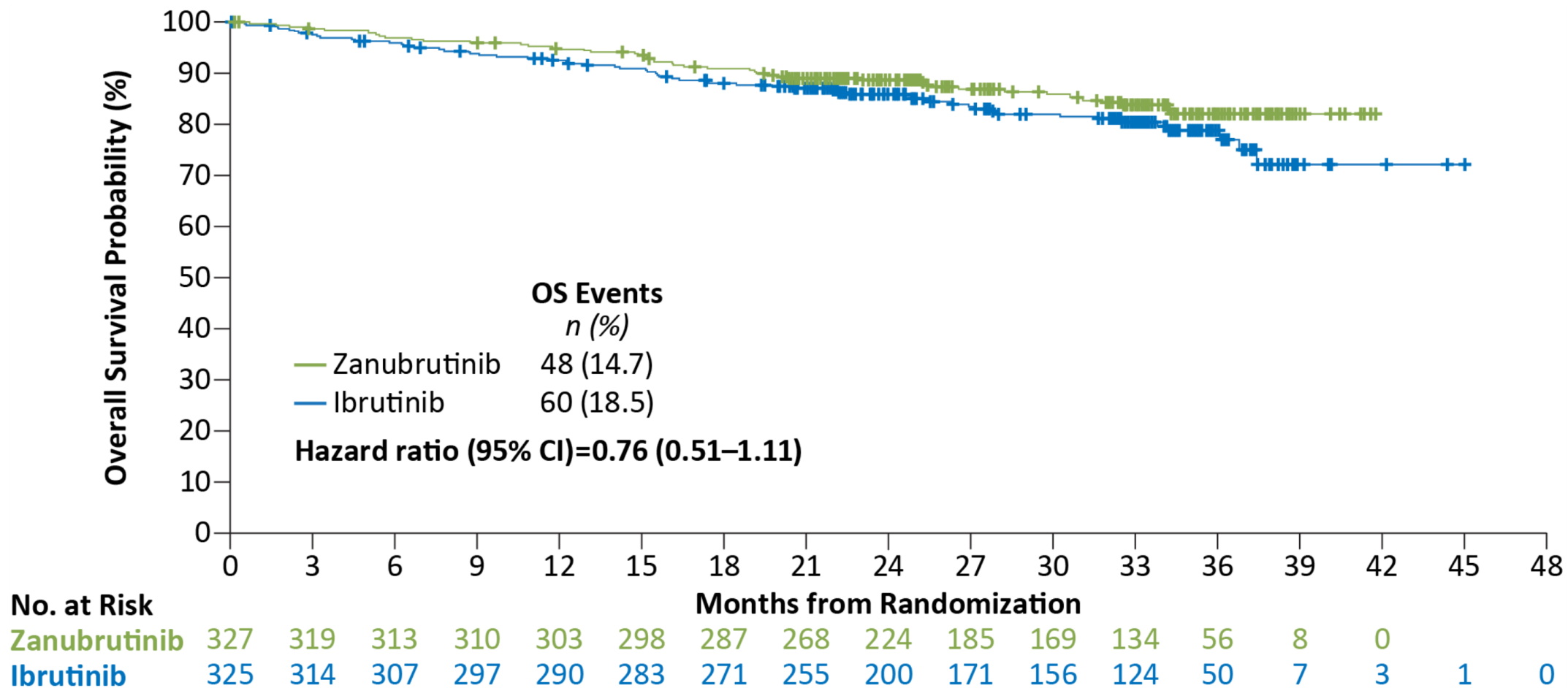


PFS data assessed by IRC

Data cutoff: 8 Aug 2022

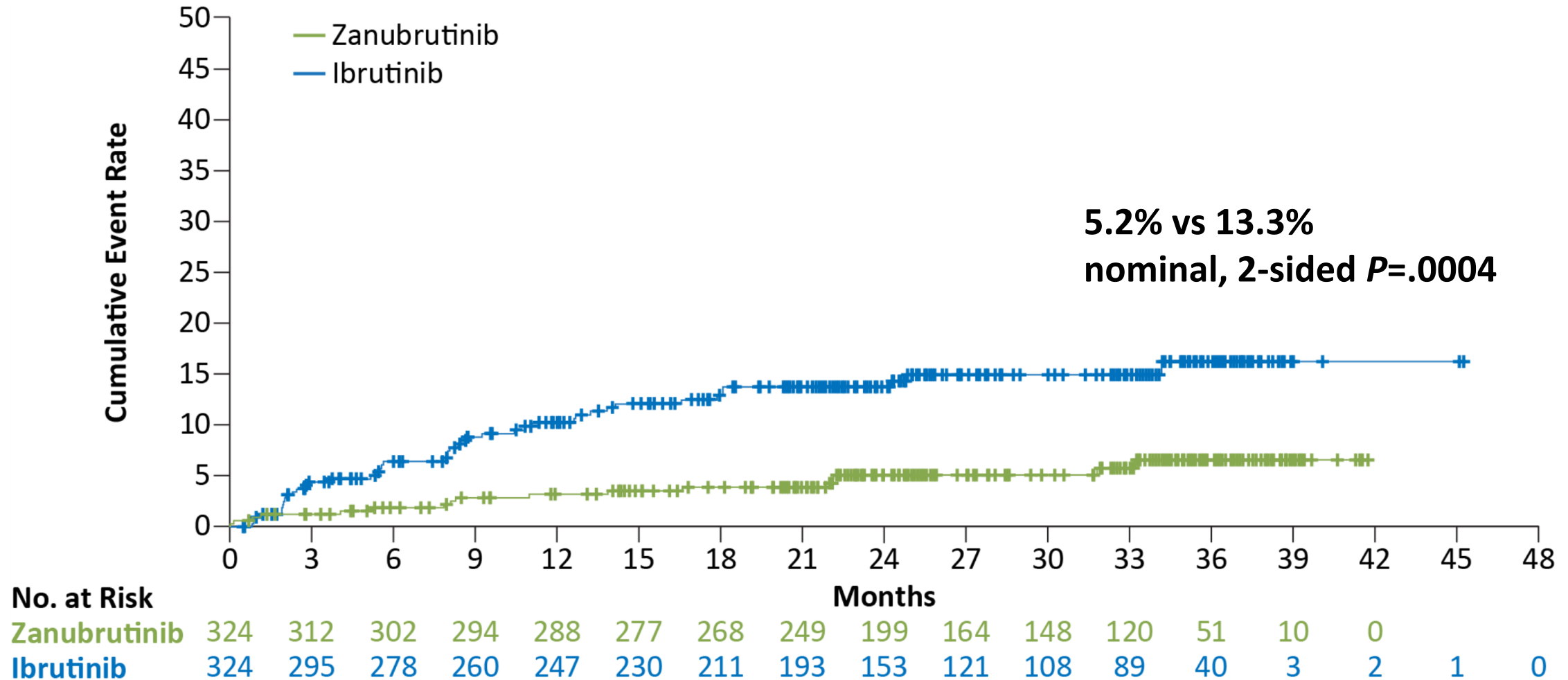
Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib



Data cutoff: 8 Aug 2022

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



Data cutoff: 8 Aug 2022

Case #2

76-year-old man with CLL treated with venetoclax for the past 18 months presents with increasing lymphadenopathy and fatigue. Prior treatment includes BR, R-CHOP, ibrutinib, and venetoclax plus rituximab (VenR). On physical exam, he has an 8×6 cm left axillary lymph node. Labs show WBC 3.22 K/mcL (ALC 0.44 K/mcL, ANC 2.12 K/mcL), HGB 10.4 g/dL, PLT 111 K/mcL, β 2M 5.2 mg/L, and LDH 256 U/L. CT-PET showed diffuse LAD with SUV_{max} 4.41 in left axillary lymph node.



Question #2

What would you consider for next treatment (including clinical trials)?

- A. BGB-11417 (Novel BCL2 inhibitor)
- B. Idelalisib + rituximab
- C. MS-533 (PKC-beta inhibitor)
- D. NX-2127 (BTK degrader)
- E. Pirtobrutinib



Question #2

What would you consider for next treatment (including clinical trials)?

- A. BGB-11417 (Novel BCL2 inhibitor)
- B. Idelalisib + rituximab
- C. MS-533 (PKC-beta inhibitor)
- D. NX-2127 (BTK degrader)
- E. Pirtobrutinib

Abstracts

Pirtobrutinib in CLL previously treated with covalent BTKi

BTK degrader NX-2127 in R/R CLL

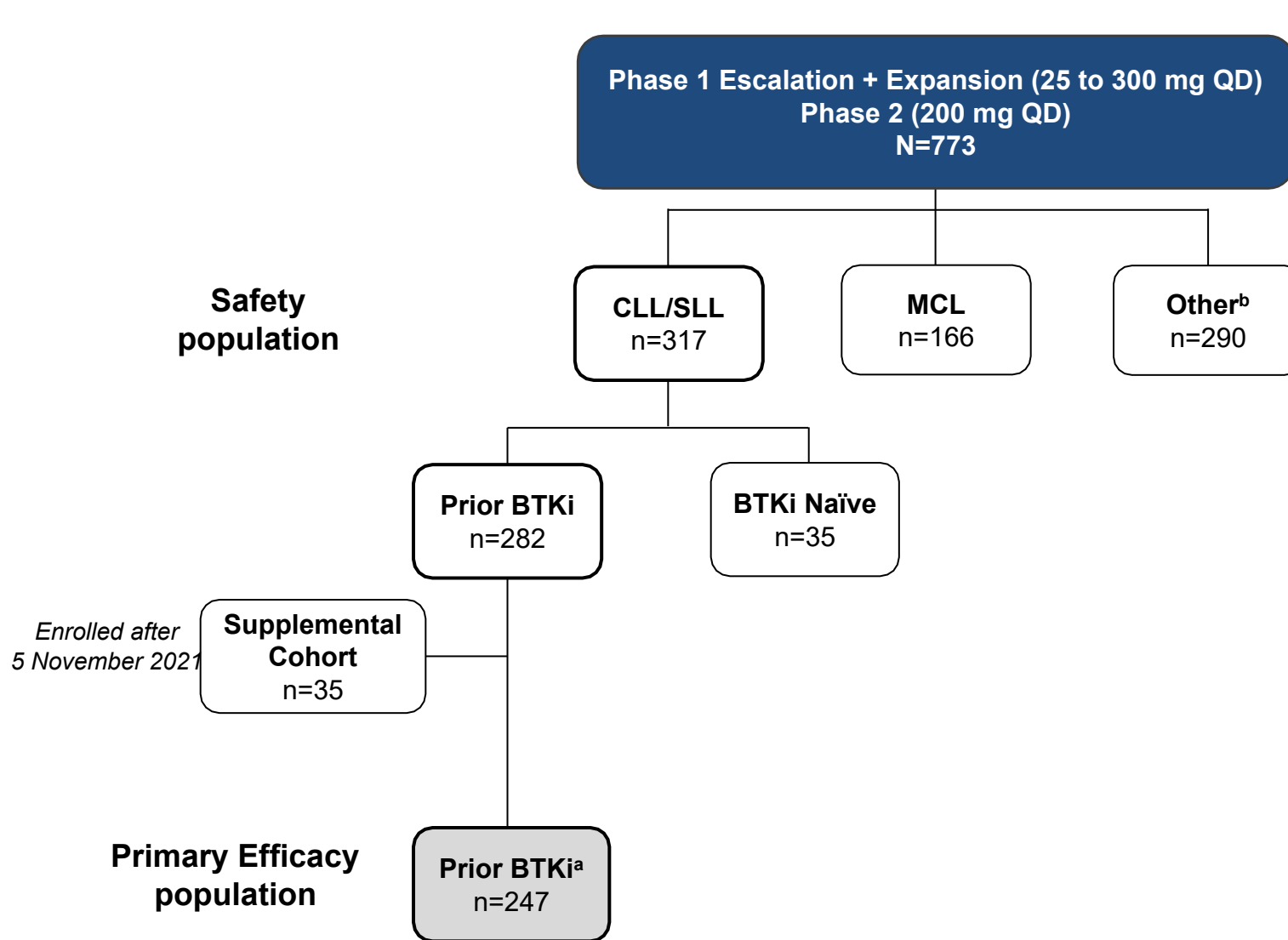


Efficacy of Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated Relapsed / Refractory CLL/SLL: Additional Patients and Extended Follow-up from the Phase 1/2 BRUIN Study

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Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (iwCLL) as assessed by IRC

Primary efficacy population^a

- Enrolled in phase 1 or 2
- Treated with prior BTK inhibitor containing regimen
- Received one or more doses of pirtobrutinib monotherapy

DOR, duration of response; ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MTD, maximum tolerated dose; IRC, independent review committee; QD, daily; Data cutoff date of 29 July 2022. ^aTo ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. ^bOther includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

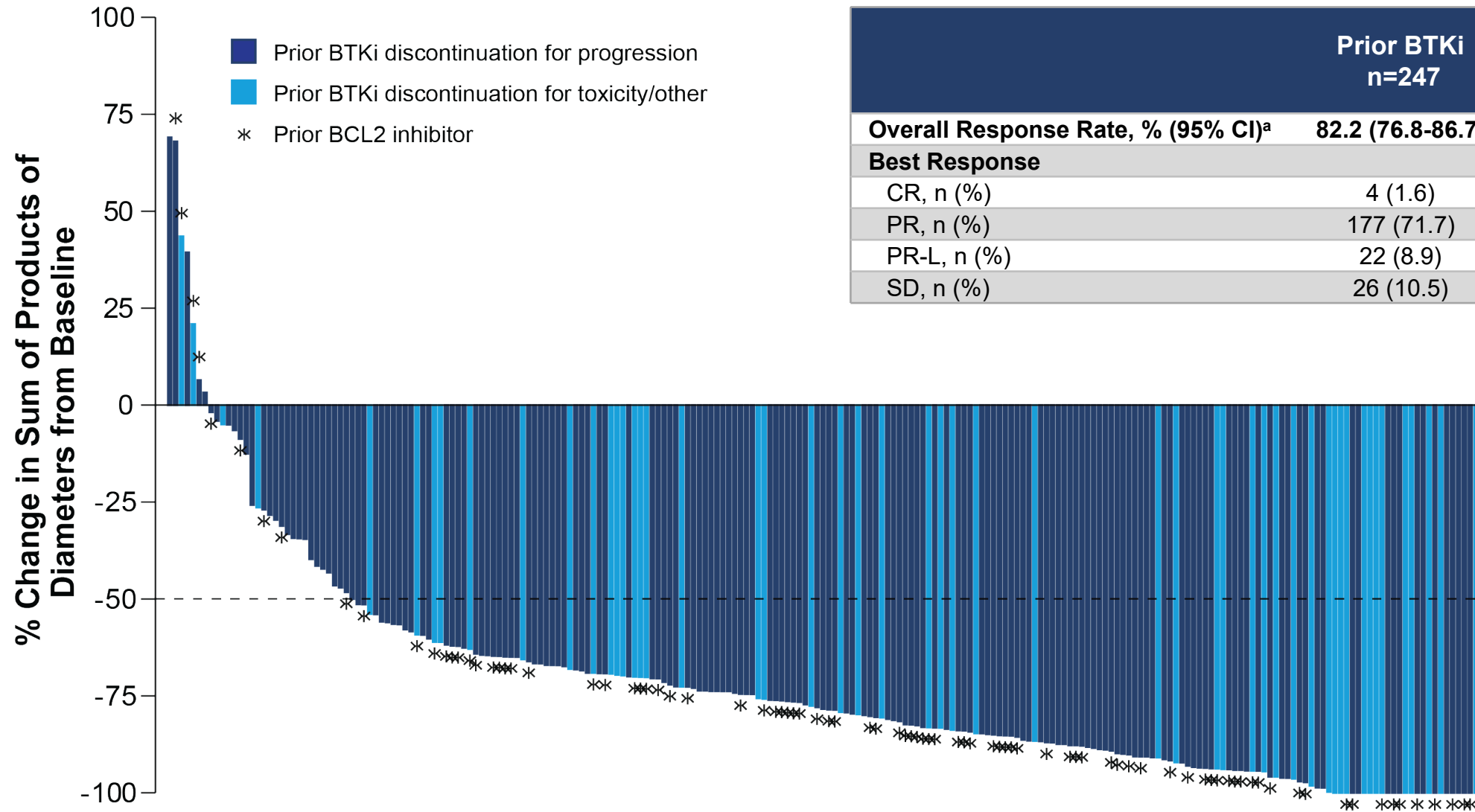
CLL/SLL Patient Characteristics

Characteristics	n=247
Median age, years (range)	69 (36-88)
Male, n (%)	168 (68)
Histology	
CLL	246 (>99)
SLL	1 (<1)
Rai staging ^a	
0-II	131 (53)
III-IV	102 (41)
Bulky Disease ≥5 cm, n (%)	78 (32)
ECOG PS, n (%)	
0	133 (54)
1	97 (39)
2	17 (7)
Median number of prior lines of systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	247 (100)
Anti-CD20 antibody	217 (88)
Chemotherapy	195 (79)
BCL2 inhibitor	100 (41)
PI3K inhibitor	45 (18)
CAR-T	14 (6)
Allogeneic stem cell transplant	6 (2)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)

Baseline Molecular Characteristics ^b	
Mutation status, n/n available (%)	
<i>BTK</i> C481-mutant	84/222 (38)
<i>BTK</i> C481-wildtype	138/222 (62)
<i>PLCG2</i> -mutant	18/222 (8)
<i>PLCG2</i> -wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	
17p deletion	51/176 (29)
<i>TP53</i> mutation	87/222 (39)
17p deletion and/or <i>TP53</i> mutation	90/193 (47)
Both 17p deletion and <i>TP53</i> mutation	48/170 (28)
<i>IGHV</i> unmutated	168/198 (85)
Complex Karyotype	24/57 (42)
11q deletion	44/176 (25)
Reason for prior BTKi discontinuation ^c , n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; Data cutoff date of 29 July 2022. ^a14 patients had missing data for Rai staging data. ^bMolecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control. ^cIn the event more than one reason was noted for discontinuation, disease progression took priority.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment

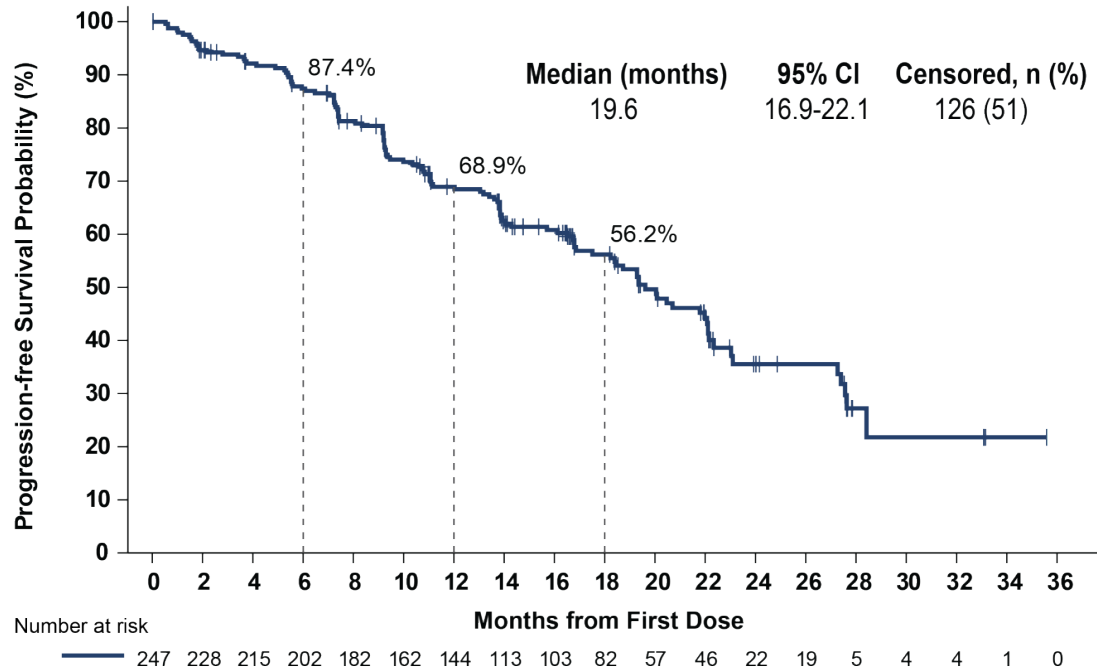


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)^a	82.2 (76.8-86.7)	79.0 (69.7-86.5)
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

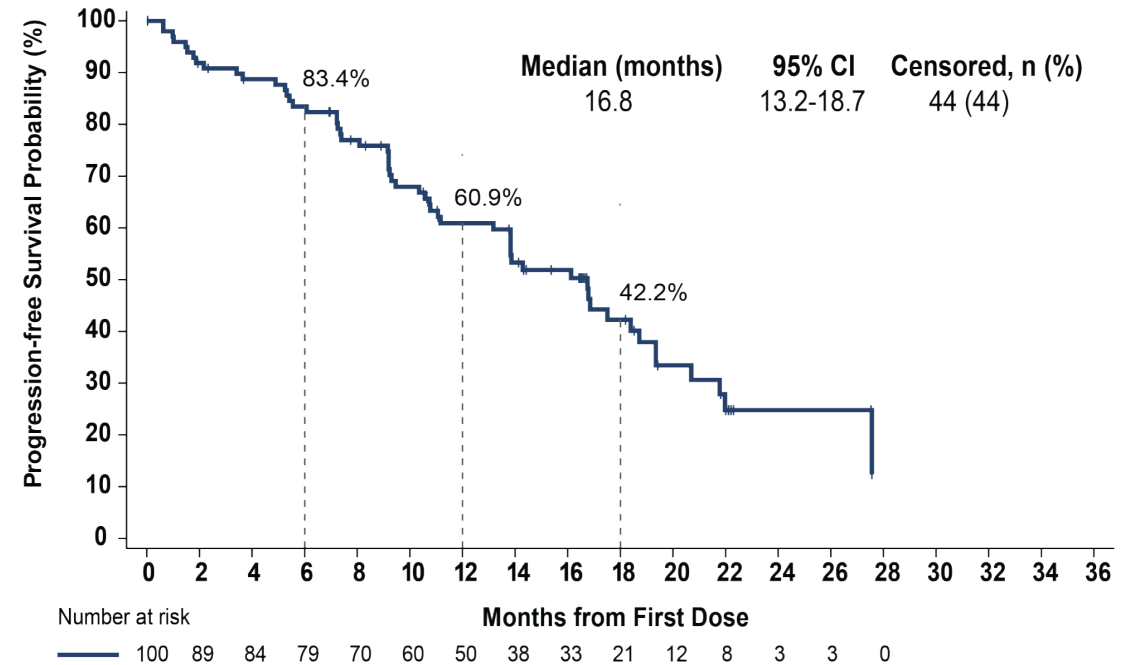
Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. ^aORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 19.4 months for patients who received prior BTKi

- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Pirtobrutinib Safety Profile

CLL/SLL (n=317)				
Adverse Event (AEs)	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	31.5%	1.9%	3.5%	0.3%
Neutropenia ^a	32.5%	26.8%	19.6%	14.8%
Diarrhea	26.5%	0.6%	8.8%	0.3%
Contusion	24.3%	0.0%	16.4%	0.0%
Cough	24.3%	0.0%	1.6%	0.0%
Covid-19	24.0%	5.0%	1.6%	0.0%
Nausea	18.9%	0.0%	3.2%	0.0%
Abdominal pain	18.0%	1.6%	2.2%	0.3%
Dyspnea	17.4%	0.9%	0.6%	0.0%
Headache	17.4%	0.6%	5.4%	0.3%
Upper respiratory tract infection	16.4%	0.3%	3.5%	0.0%
Back pain	16.1%	0.9%	0.9%	0.0%
Anemia	15.1%	8.8%	4.7%	2.2%
AEs of Special Interest ^b	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising ^c	30.3%	0.0%	19.6%	0.0%
Rash ^d	17.0%	0.3%	5.7%	0.3%
Arthralgia	18.3%	0.9%	4.1%	0.0%
Hemorrhage/Hematoma ^e	12.3%	2.2%	4.1%	0.9%
Hypertension	14.2%	3.5%	3.8%	0.3%
Atrial fibrillation/flutter ^{f,g}	3.8%	1.3%	1.3%	0.3%

Median time on treatment for the CLL/SLL safety population was 16.5 months

Discontinuations due to treatment-related AEs occurred in 2.8% (n=9) of CLL/SLL patients

Dose reductions due to treatment-related AEs occurred in 4.7% (n=15) of CLL/SLL patients

Data cutoff date of 29 July 2022. ^aAggregate of neutropenia and neutrophil count decreased. ^bAEs of special interest are those that were previously associated with covalent BTK inhibitors. ^cAggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. ^dAggregate of all preferred terms including rash. ^eAggregate of all preferred terms including hematoma or hemorrhage. ^fAggregate of atrial fibrillation and atrial flutter. ^gOf 12 total afib/aflutter TEAEs in the CLL/SLL safety population, 3 occurred in patients with a prior medical history of atrial fibrillation.

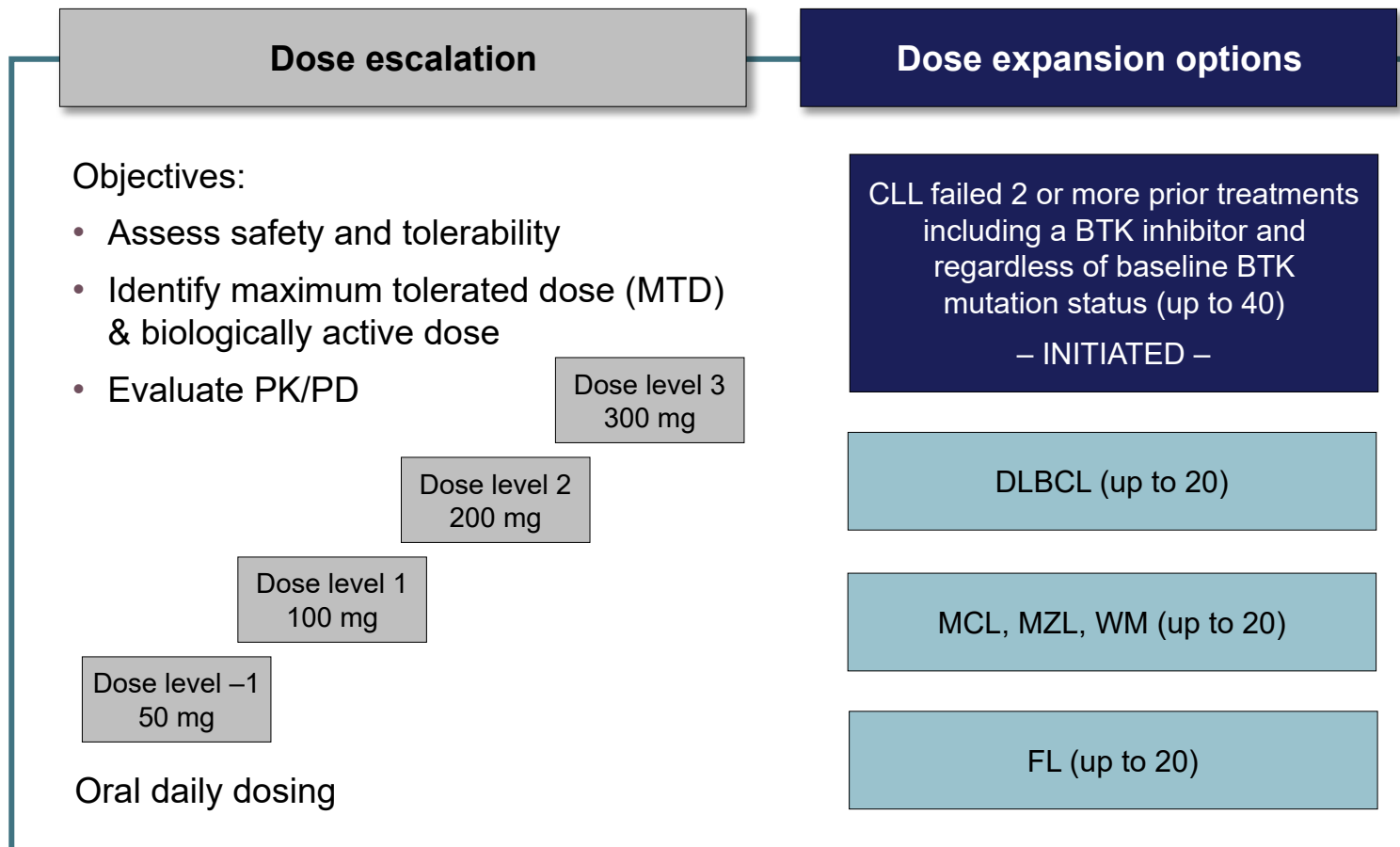
NX-2127-001, a first-in-human trial of NX-2127, a Bruton's Tyrosine Kinase-targeted protein degrader, in patients with relapsed or refractory chronic lymphocytic leukemia and B-cell malignancies

Anthony Mato,¹ William G. Wierda,² Weiyun Ai,³ Ian Flinn,⁴ Michael Tees,⁵ Manish R. Patel,⁶ Krish Patel,⁷ Susan O'Brien,⁸ David Bond,⁹ Lindsey E. Roeker,¹ Tanya Siddiqi,¹⁰ Michael Wang,² Clare Sun,¹¹ Omar Abdel-Wahab,¹ Amanda Schwab,¹² May Tan,¹² Erin Meredith,¹² Melissa A. Gessner,¹² Adrian Wiestner,¹¹ Alexey Danilov¹⁰

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NX-2127-001: trial design

Phase 1 trial in adults with relapsed/refractory B-cell malignancies



- CLL Phase 1b expansion cohort at 100 mg dose
 - MTD not established
 - 100 mg dose chosen as expansion dose based on PD, clinical activity and safety profile
- Phase 1a dose escalation is ongoing at 200 mg and 300 mg doses for patients with NHL (e.g. DLBCL, MCL, MZL, WM, FL)

NX-2127 safety summary (TEAEs >15% in all patients)

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=36)	Grade 3+ (N=36)	SAE (N=36)
Fatigue	19 (52.8)	–	-
Neutropenia ^a	14 (38.9)	13 (36.1)	-
Contusion ^b	10 (27.8)	–	1 (2.8)
Thrombocytopenia ^c	9 (25)	3 (8.3)	-
Anemia	8 (22.2)	4 (11.1)	1 (2.8)
Hypertension	9 (25.0)	1 (2.8)	-
Constipation	7 (19.4)	–	-
Dyspnea	7 (19.4)	1 (2.8)	-
Pruritis	7 (19.4)	–	-
Atrial fibrillation/Atrial flutter ^d	6 (16.7)	3 (8.3)	2 (5.6)
Diarrhea	6 (16.7)	–	-
Petechiae	6 (16.7)	–	-
Rash	6 (16.7)	–	-

^aAggregate of "neutropenia" and "neutrophil count decreased"^bContusion includes episodes of bruising and other similar terms ^cAggregate of "thrombocytopenia" and "platelet count decreased" ^dCases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)

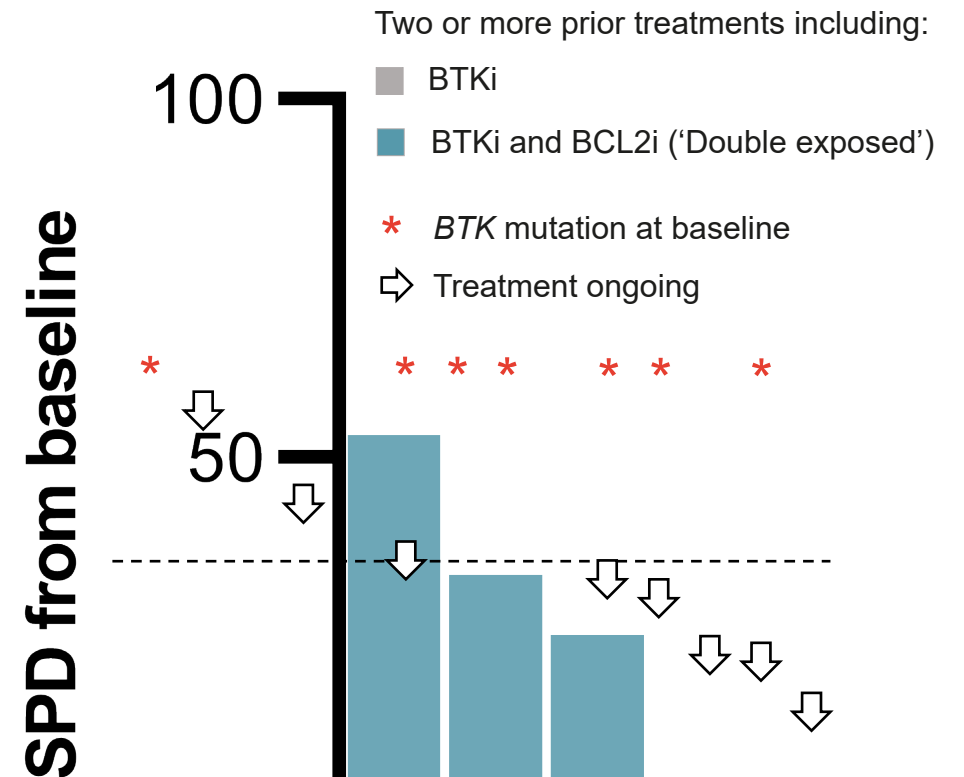
1 DLT of cognitive disturbance was observed at 300 mg (CLL); MTD not reached

NX-2127 preliminary efficacy (patients with CLL)

Disease-evaluable patients	n=15
Objective response rate, ^a % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE ^b	3 (20)

^aObjective response rate includes CR + CRi + nPR + PR-L + PR

^bPatients who discontinued after a single assessment of SD are considered as NE



*One patient, not shown above, with prior BTKi and BCL2i treatment and with a *BTK* mutation detected at baseline, had no nodal disease at baseline. Their treatment is ongoing with a PR

Case #3

69-year-old woman with Richter transformation presents for follow-up. She was previously treated with FCR for CLL and was diagnosed with transformation to DLBCL after 6 months on acalabrutinib. She received pembrolizumab (discontinued for pneumonitis) then R-EPOCH, achieving complete metabolic response. She is anxious about disease relapse and would like to know about her future treatment options.



Question #3

What are treatment options for Richter transformation?

- A. Allogeneic stem-cell transplant
- B. CAR-T
- C. Pirtobrutinib
- D. T-cell engaging bispecific antibodies
- E. Venetoclax + R-EPOCH



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Abstracts

Phase 1/2 study of pirtobrutinib in RT

Phase 1b/2 study of epcoritamab in RT



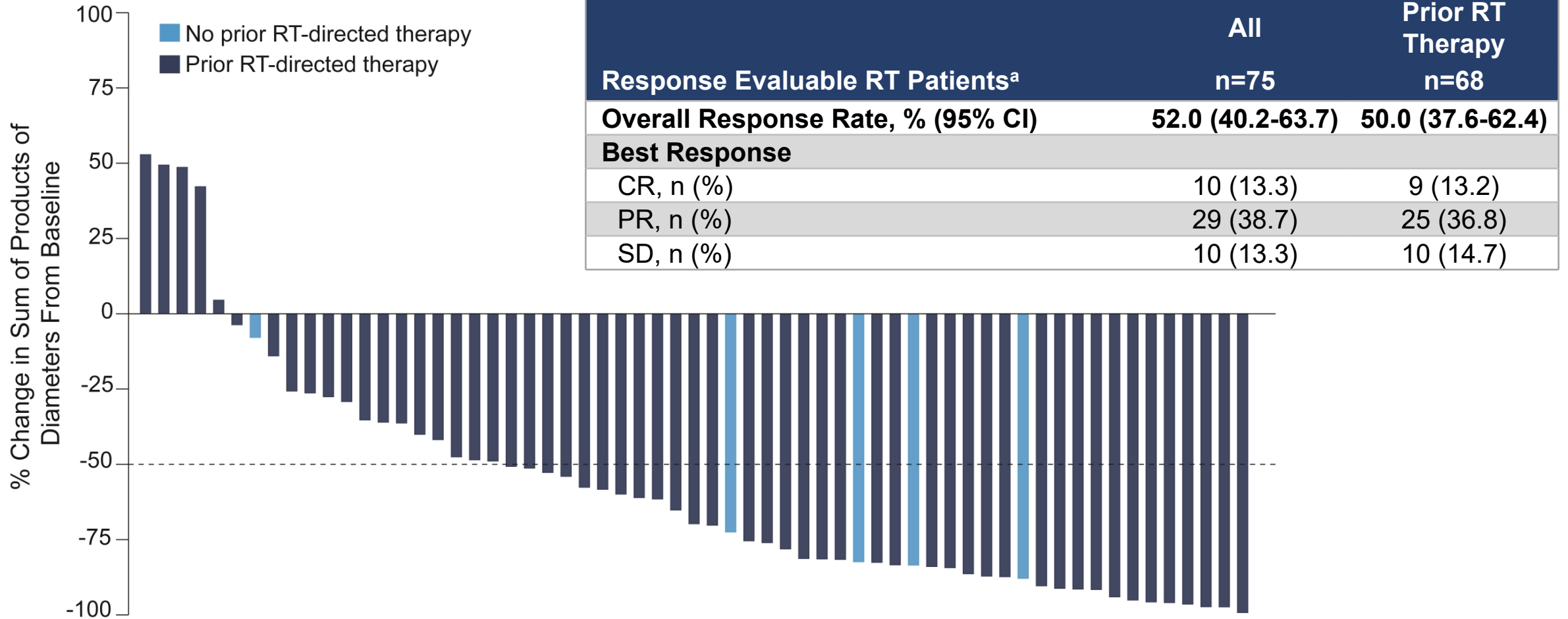
Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results From the Phase 1/2 BRUIN Study

William G. Wierda¹, David Lewis², Paolo Ghia³, Nirav N. Shah⁴, Catherine C. Coombs⁵, Chan Y. Cheah⁶, Jennifer Woyach⁷, Nicole Lamanna⁸, Joanna M. Rhodes⁹, Marc S. Hoffmann¹⁰, Shuo Ma¹¹, Toby A. Eyre¹², Talha Munir¹³, Manish R. Patel¹⁴, Alvaro J. Alencar¹⁵, Constantine S. Tam¹⁶, Wojciech Jurczak¹⁷, Ewa Lech-Maranda¹⁸, John F. Seymour¹⁶, Lindsey E. Roeker¹⁹, Philip A. Thompson¹, Paolo B. Abada²⁰, Chunxiao Wang²¹, Amy S. Ruppert²¹, Binoj Nair²⁰, Hui Liu²⁰, Donald E. Tsai²⁰, Anthony R. Mato¹⁹

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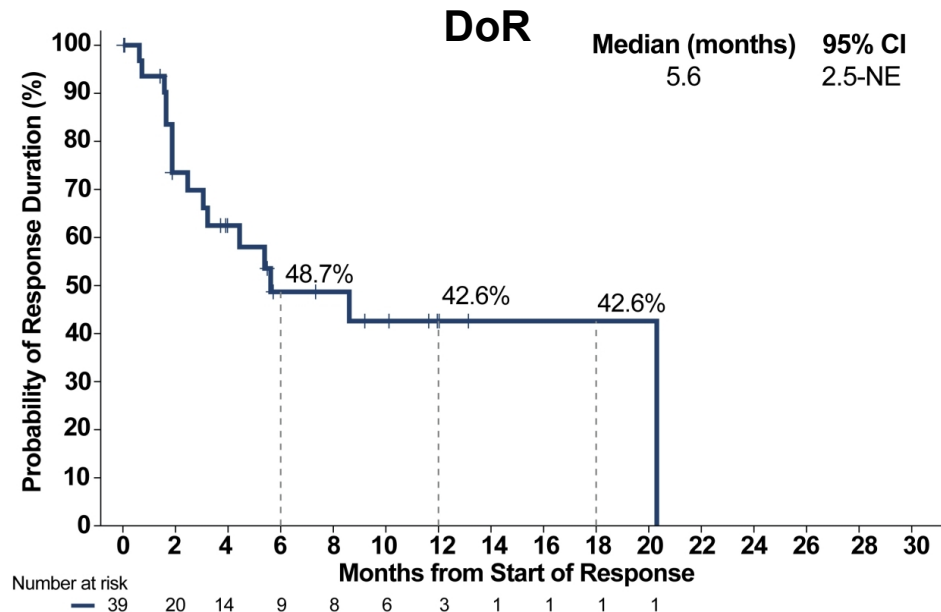
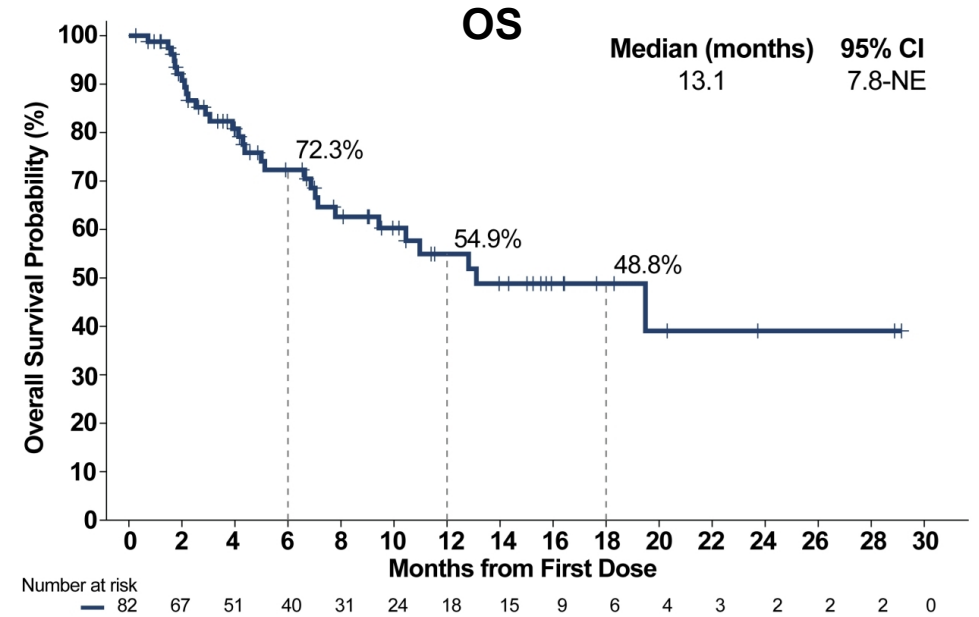
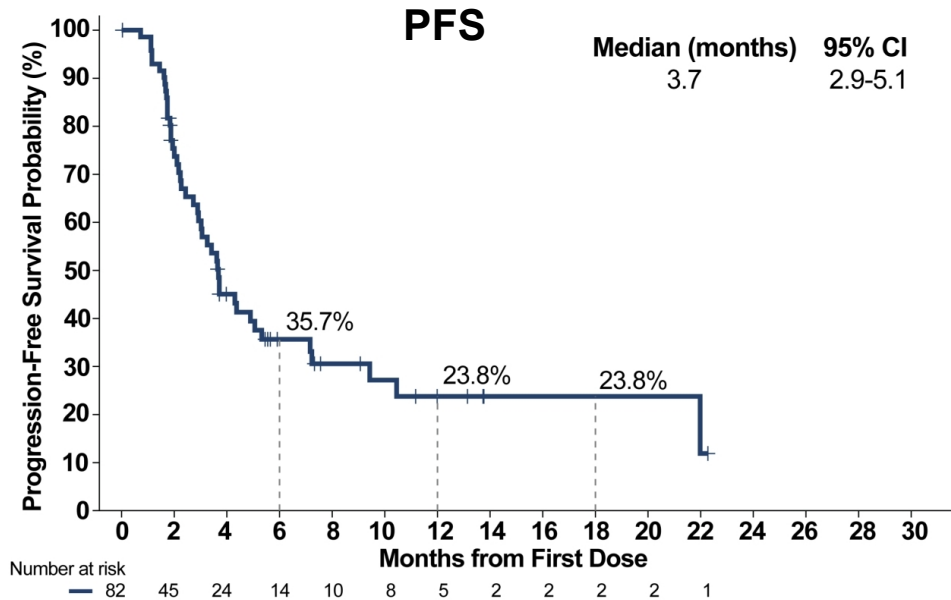
Pirtobrutinib Efficacy in RT Patients

No central pathology review



- Among 75 response-evaluable patients, the median time-to-response was 1.8 months (range, 0.9-9.2), median time on study was 6.7 months (range, 0.7-29.1), and median time on treatment was 3.4 months (range, 0.2-26.7)

PFS, OS, and DoR in All RT Patients



- 6 responding patients were censored for curative intent transplant therapy

Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1)

Arnon P. Kater, MD, PhD,¹ Jing Christine Ye, MD,² Jose Sandoval-Sus, MD,³ Mar Bellido, MD, PhD,⁴ Jacob Haaber Christensen, MD, PhD,⁵ Anthony R. Mato, MD, MSCE,⁶ Ann Janssens, MD, PhD,⁷ Toshihiko Oki, MD, PhD,⁸ Daniela Hoehn, MD, PhD,⁹ Marcia Rios, MBA,⁹ Alexandra Kuznetsova, PhD,¹⁰ Rebecca Valentin, MD, PhD,¹⁰ Herbert Eradat, MD¹¹

¹Amsterdam UMC, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, Netherlands; ²Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA; ³Moffitt Cancer Center at Memorial Healthcare System, Pembroke Pines, FL, USA; ⁴University Medical Center Groningen and University of Groningen, Groningen, Netherlands; ⁵Odense University Hospital, Odense, Denmark; ⁶Memorial Sloan Kettering Cancer Center, Chronic Lymphocytic Leukemia Program, New York, NY, USA; ⁷University Hospitals Leuven, Leuven, Belgium; ⁸AbbVie, North Chicago, IL, USA; ⁹Genmab, Princeton, NJ, USA; ¹⁰Genmab, Copenhagen, Denmark; ¹¹David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Study Design: EPCORE CLL-1 RS Expansion Cohort

Dose escalation

Median follow-up: 4.9 mo (range, 0.6–9.3)

CLL¹

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key RS inclusion criteria

- Ineligible for or voluntarily declined chemotherapy
- ≤1 prior line of therapy for RS-DLBCL
- Biopsy-proven transformation to CD20⁺ RS-DLBCL
- Prior clinical history of CLL or SLL
- ECOG PS 0–2
- Measurable disease by PET and/or CT/MRI

RS-DLBCL expansion, N=10

Step-up dosing^a

Epcoritamab (SC)
48 mg

QW C1–3
Q2W C4–9
Q4W C10+

Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter

Treatment until disease progression

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first 4 doses of epcoritamab
- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete metabolic response (CMR) rate, time to response (TTR), and safety/tolerability

Data cutoffs: September 8, 2022 (efficacy); September 16, 2022 (safety). Epcoritamab was administered in 28-d cycles as shown.^aPatients received SC epcoritamab with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS.¹ Kater AP, et al. ASH 2021. Abstract 2627.

Best Overall Response

Response, n (%) ^a	Total Efficacy Evaluable N=10
Overall response^b	6 (60)
Complete metabolic response (CMR)	5 (50)
Partial metabolic response (PMR)	1 (10)
Stable disease	1 (10)
Progressive disease	2 (20)
Not evaluable	1 (10) ^c

Data cutoff: September 8, 2022. Median follow-up: 4.9 mo (range, 0.6–9.3).

^aBased on modified response-evaluable population, defined as patients with ≥ 1 target lesion at baseline and ≥ 1 postbaseline response evaluation and/or patients who died within 60 d of first dose. ^bResponse assessment according to Lugano 2014 criteria. ^cPatient stopped treatment on C1D15 due to progression and did not receive any scans.

High overall and complete metabolic response rates observed

Conclusions

- Zanubrutinib has improved efficacy and safety compared to ibrutinib in R/R setting
- Fixed duration Ibr + Ven achieves deep and durable remissions in the front-line setting
- Novel agents targeting BCR signaling and BCL2 in clinical development
- Promising data for Richter transformation, but will likely require combination therapy for durable remissions

